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THE AMERICAN JOURNAL
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DECEMBER, 1948

ORIGINAL ARTICLES

THE MILLIKAN OXIMETER IN THE RECOGNITION AND TREATMENT OF ANOXEMIA IN CLINICAL MEDICINE

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THE accurate methods available for determining a given patient's need for oxygen therapy, and for assessing the results of oxygen administration, have been too cumbersome for general use at the bedside. The attending physician has been forced to use one or more of the following rather crude indications: (a) The presence of a disease which may produce anoxemia, (b) The presence of dyspnea, (c) The presence of visible cyanosis (sometimes difficult to assess accurately),[3] and (d) The apparent clinical response to a trial of oxygen therapy.

The Millikan Oximeter[9] affords a simple and accurate means for determining the changes in arterial oxygen saturation, at the bedside, without the discomfort of arterial puncture, or the difficulties of conventional gas analysis. We have used it on the medical wards of the Hospital of the University of Pennsylvania to assess the need for oxygen therapy in the individual patient, and to determine the method of oxygen administration best suited to his needs.

Methods. *1. The Oximeter:* The oximeter consists essentially of a small "ear unit" and a galvanometer. The ear piece contains an electric bulb, light filters, and a photo-electric cell. It fits over the pinna of the ear with the bulb in front, the filters and cell behind. The heat generated by the bulb dilates the arterioles of the ear and increases the blood flow sufficiently to make the ear blood equal, in oxygen content, to arterial blood. The light generated by the bulb penetrates the ear and strikes the photo-electric cell. The filters and cell have such characteristics that variations in the amount of oxyhemoglobin within the blood vessels of the ear are recorded continuously on the galvanometer. Present models of the instrument cover only half the potential range of saturation; hence the galvanometer is graduated from 50 to 100%. There is a time lag of 5 seconds in the

galvanometer. With these limitations, Millikan has shown by comparison with hundreds of simultaneous arterial punctures, that the instrument is accurate within 3 to 7%.[9]

Although percentage changes in oxygenation can be read directly from the instrument, absolute values can only be obtained by one of two procedures: (a) while a normal subject is breathing 100% oxygen, the galvanometer is adjusted to a reading of 100%; subsequent changes in the same subject during the same experiment will be shown in absolute figures; (b) with an abnormal subject whose capacity to oxygenate his blood completely in an atmosphere of pure oxygen is questionable, one must set the galvanometer at some arbitrary figure and take one simultaneous arterial blood sample for gas analysis; the mathematical difference between the arbitrary setting and the actual saturation at that moment can then be used as a constant factor for correcting subsequent readings during the same run.[10]

In the following experiments, method (a) was used in all normal subjects. In some abnormal subjects (Cases 26 and 36, and in a patient with the Tetralogy of Fallot, not included in the Tables) method (b) was used. In the remainder, the oximeter readings were recorded without a simultaneous determination of arterial oxygen saturation. This limited our ability to assess the original degree of anoxemia in these subjects. However, as will be indicated below, the percentage rise in the oximeter reading following oxygen therapy, in addition to affording an accurate method of assessing the effects of oxygen administration, permits certain deductions concerning the presence of anoxemia.

2. Subjects: A total of 46 individuals was studied. Ten of these were hospital employees or patients who showed no clinical evidence of anoxemia or of any disease which might interfere with the oxygenation of the blood. The remaining 36 were considered to be potentially or actually anoxemic as a result of diseases of the heart, lungs, or both. These subjects were classified accordingly as: I. "normals"; II. cardiac disease; III. pulmonary disease; and IV. mixed. This classification was made on the basis of the clinical findings, supported, in a few instances, by information obtained at necropsy. Obviously there is considerable overlapping in the last 3 groups; since there is usually some pulmonary involvement in advanced cardiac disease and vice versa. In each instance the assignment to a group depended on our estimate as to which factor was the predominant cause of the anoxemia.

3. Procedure: With the patient at rest in bed or in a wheel chair and breathing room air, the oximeter was attached to the ear. After the bulb was lit, 15 minutes were allowed to elapse to permit "warming up" of the instrument and full dilation of the ear vessels. Pulse rates and respiratory rates, blood pressure readings, and circulation times* (Decholin arm-tongue) were determined during this basal period. At the end of the 15 minutes, the galvanometer was adjusted to the clinically estimated arterial saturation (from 96% in the normal group down to 60% in very cyanotic individuals). Oxygen was then administered and the galvanometer readings recorded every 15 seconds until there was no further change. The maximum rise was reached within 5 minutes in all but a very few instances, and could be maintained indefinitely. After continuing oxygen administration from 5 to 60 minutes, it was discontinued abruptly and the rate and degree of fall in the oximeter reading was recorded. Pulse, respiration, and blood pressure were checked repeatedly throughout the test.

Since our main purpose was to compare the maximal rise in arterial oxygen in different individuals, it was necessary to administer to all a uniform and high concentration of oxygen. The B. L. B. (Boothby, Lovelace, Bulbulian,[2]) mask proved an acceptable method for doing this. Direct measurements of samples withdrawn from the mask showed an oxygen concentration of 90 to 97%. All of the graphs and most of the data reported here are based on the rise in oximeter reading observed when the pa-

* In 18 of the 36 abnormal patients.

tient suddenly changed from breathing room air to breathing oxygen through a B. L. B. mask.

In most subjects the test described above was repeated several times on the day of the first experiment. In many, it was repeated on several occasions subsequently, in order to correlate changes in the oximeter response with changes in the patient's condition.

In certain instances in addition to the routine test with the B. L. B. mask, oxygen was administered in lower concentrations, and the oximeter response was compared to that of the routine test. The Lambertson-Godfrey hood[8] was used in a number of such experiments and proved capable of delivering controlled concentrations ranging from 30 to 85% by direct measurement. Oxygen was administered by nasal catheter in a number of other instances. We assumed that an oxygen inflow of 7 liters per minute by nasal catheter properly placed in the oropharynx gave an inspired oxygen concentration of from 40 to 50%.[1a]

4. Terminology: In the rest of this paper we will use the following terminology. (1) A subject's *"oximeter response"* signifies the rise in the galvanometer reading when he changes from breathing room air to breathing 90 to 97% oxygen in a B. L. B. mask.

(2) A *"normal oximeter response"* is a rise of 5% or less. A *normal oximeter response* does not rule out anoxemia (see discussion).

(3) An *"increased oximeter response"* is a rise of more than 5%. This we take as an indication of anoxemia, *i.e.*, that the arterial oxygen must have been below 95% while the subject was breathing room air.

Results. *1. Normals* (10 subjects). The patients in this group ranged in age from 16 to 71 years, four having been 50 or over. Two of the older patients had peripheral vascular disease, and another was moderately hypertensive. None had symptoms nor showed any signs of cardiac failure or pulmonary disease. On breathing 90 to 97% oxygen from the B. L. B. mask, the maximal increase in arterial saturation (oximeter response) ranged from 2 to 5 %.† This "normal" range is blocked out in all of the following figures as a standard of comparison.

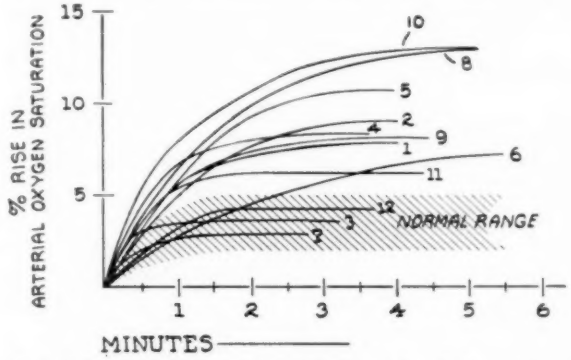

FIG. 1.—Acute Cardiac Infarction. The numbers at the ends of the curves refer to the cases of this sub-group.

2. Cardiac Disease (22 patients). This group is subdivided into (a) Acute Cardiac Infarction and (b) Congestive Heart Failure.

(a) *Acute Cardiac Infarction* (Figure 1) (12 patients; Cases 1 to 12). The patients in this group had typical histories and characteristic clinical and electrocardiographic findings of acute myocardial infarction. In 3, the diagnosis was confirmed at necropsy. These 12 patients were selected solely on the basis of their diagnosis, not because they had clinical evidence of anoxemia. As shown in Figure 1, their oximeter responses varied from 3 to 13%. Nine, or 75%, showed an increased oximeter response. Pulmo-

†Comroe and others[4,5,6] have done a similar test on a larger series of normals and have demonstrated a slightly greater range (2 to 6%).

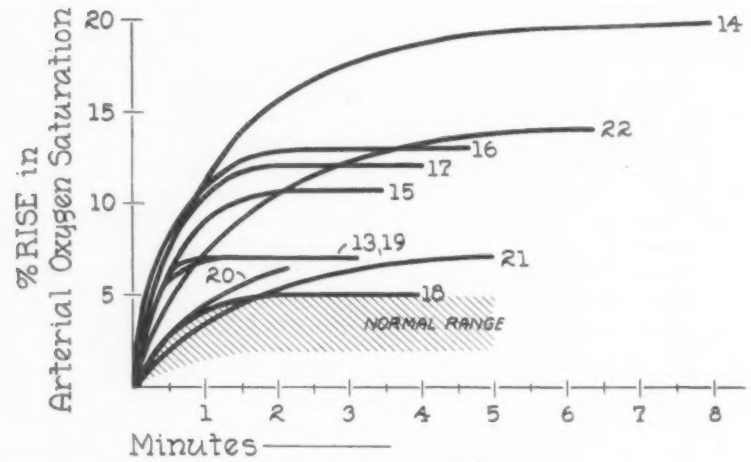

FIG. 2.—Congestive Heart Failure

nary congestion (6 cases) and, or, shock (3 cases) were the 2 most obvious factors which were present and possibly responsible for the anoxemia in these subjects. Of the 3 patients having responses of 10% or more, Case 5 was in shock with marked pulmonary edema, Case 8 was in shock, his lungs were clear to physical examination, Case 10 was in moderately severe congestive heart failure with pulmonary congestion. However, 4 patients (Cases 1, 6, 9, 11) showed an increased oximeter response (*i. e.* anoxemia) without demonstrable signs of shock or more than a few râles at the lung bases. We were unable to find any means of predicting the oximeter response in these patients. Moreover, there was no constant correlation between the oximeter response and cyanosis, pulse rate, respiratory rate, or precordial pain.

(b) *Congestive Failure* (Figure 2)(10 patients; Cases 13 to 22). Valvular disease, old myocardial infarction, and

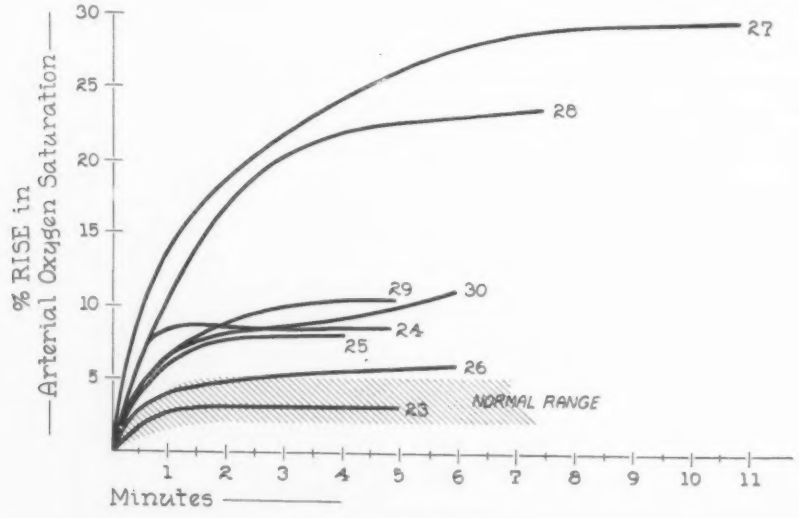

FIG. 3.—Pulmonary Disease

hypertension were the underlying causes of congestive failure in these patients. Five of them showed an oximeter response of from 10 to 20%; four rose from 6 to 10%; only one had a response within the normal range (5%). All those individuals whose response was greater than 10% were moderately to markedly cyanotic before being given oxygen. However, others who appeared to be equally cyanotic did not respond in this manner.

We were unable to find any criterion, such as cyanosis, pulmonary congestion, dyspnea, or orthopnea, which would enable us to predict reliably the degree of response. For instance, Patients 13 and 14 were quite similar in their clinical manifestations. Patient 13 was a man of 56 years with hypertension and pulmonary edema; Patient 14 was 65 years of age with degenerative heart disease and pulmonary congestion. Both were cyanotic and orthopneic. Patient 14 showed a 20% response. Patient 13 gave a 7% response.

Three patients, whose responses exceeded 10%, died, while only one, whose rise was under 10%, succumbed.

3. *Pulmonary Disease* (Figure 3) (8 patients: Cases 23 to 30). All these patients showed clinical and X-ray evidence of disease of the lungs. On the basis of their oximeter response, they may be divided into 2 groups: (a) four whose response was less than 10%, and (b) four whose response was greater than 10%. The 4 with less than 10% response all had chronic pulmonary disease. All complained of a marked limitation of their exercise tolerance, but none had dyspnea or cyanosis at rest. Three of these (Patients 24, 25, 26) had emphysema. The fourth (Patient 23) had extensive bilateral silicosis.

All of the patients who showed responses of 10% or more had cyanosis,

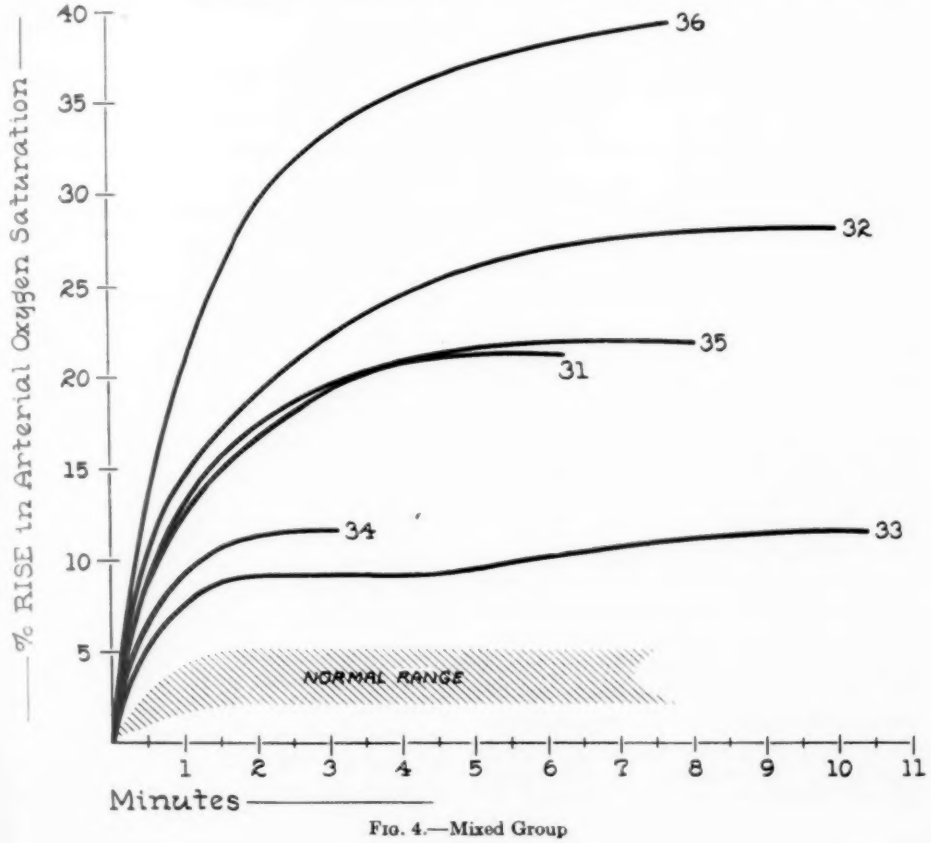

FIG. 4.—Mixed Group

orthopnea, and tachypnea. Subject 27 had severe emphysema and bilateral bronchopneumonia. Patient 28 had a spontaneous pneumothorax with 30% collapse of the right lung complicating a chronic lesion at the right base which was thought to be due to either congenital cystic disease or bronchiectasis. Patient 29 had a lobar pneumonia involving the right middle and lower lobes with secondary atelectasis and pleural effusion. The fourth patient (No. 30) had an extensive bronchogenic carcinoma invading the right middle and lower lobes, confirmed at necropsy. The first 3 patients in this subgroup improved clinically with appropriate therapy and their oximeter responses diminished as they improved, while the last showed an increase in his oximeter response on a second test a few days before death.

4. Mixed Group (Figure 4) (6 patients; Cases 31 to 36). This group consists of patients with a combination of pulmonary and cardiac disease. Two subjects (Nos. 35, 36) had chronic disease of both systems, the other four were patients with chronic heart disease and acute pulmonary complications. As shown in Figure 4, all members of this group showed definitely increased oximeter responses, some of them to a very striking degree. This was not unexpected in view of the fact that all were cyanotic. Being a very heterogeneous assortment with only their anoxemia in common, no generalizations can be made regarding prognosis or treatment except for their need of oxygen. Actually the 2 with the smallest oximeter responses are the only ones who have died.

Discussion. During the war, the Millikan oximeter was used mainly in the study of normals. It has also been used in studying special types of cardiorespiratory problems.[7,11] The experiments reported in this paper demonstrate that the instrument is useful in management of patients, since it affords a simple, convenient and rapid method for assessing the results of oxygen therapy at the bedside. Direct measurements of arterial oxygen are helpful in experimenting with this instrument, and the oximeter does not entirely replace such measurements. However, when arterial puncture and gas analysis are contra-indicated or unavailable, the oximeter response in a given patient is an indicator of the

TABLE 1. OXIMETER RESPONSES WITH VARYING INSPIRED OXYGEN CONCENTRATIONS.

		B.L.B. Mask 90–97% oxygen	*Nasal Catheter 7 liters/ min. 40–50% oxygen*	*L-G Hood*	
	Case	*% response*	*% response*	*O_2 concentration insp. air*	*% response*
Myocardial Infarction	2	9	6		
	4	9.5	5		
	5	10	—	80% oxygen conc.	10
	6	7	4		
	8	13	—	80% oxygen conc.	10
	10	12	7		
	12	4	3.5		
Congestive Failure	17	14	8		
	19	7	—	80% oxygen conc.	6
	20	7	6		
Pulmonary Disease	27	30	20		
	28	20	—	60% oxygen conc.	20
				40% oxygen conc.	15
	31	20	10		
Mixed Group	33	12	8		
	34	11.5	5.5		
	36	45	—	30–38% oxygen conc.	35

degree of benefit to be expected from oxygen administration, and may be used to determine the concentration of oxygen best suited to the individual case.

The following table shows the oximeter responses obtained with varying inspired oxygen concentrations.

These figures show that, whereas in general the largest oximeter responses were obtained with the highest concentrations of inspired oxygen, certain patients (Nos. 27, 28 and 36) showed very striking responses to lower concentrations.

Thus in selected cases, the relatively low inspired oxygen concentrations such as are obtainable in an oxygen tent or by nasal catheter, appear to be therapeutically effective. However, the selection of such cases on clinical grounds alone does not seem possible.

If it had not been for the oximeter, the patient described in case report 36 might not be alive today. This 44 year old man with advanced pulmonary fibrosis had been admitted to the medical wards 4 times between March 1946 and January 1947 for congestive heart failure. In February, 1947 he was readmitted very ill with anasarca, orthopnea and cyanosis. He was tested with the oximeter and a remarkable response (45%) was obtained with 90–97% oxygen administered by B. L. B. mask. This was checked by means of chemical determinations of arterial oxygen saturation, and found to be accurate. Then by means of the oximeter it was determined that as little as 33% oxygen in the inspired air would maintain a 30% to 35% rise in the oximeter reading. Consequently, he was placed on continuous oxygen by nasal catheter at 6 liters per minute, digitalization was maintained, diuretics discontinued, and his fluid intake was not restricted. A marked clinical improvement occurred. At the end of 3 weeks he was discharged, free of edema, and with no dyspnea while walking slowly. During the eleven months since then, he has led a quiet ambulatory life at home, remaining free of congestive heart failure by using nasal oxygen throughout the night, and stopping it during the day. Digitalis has been continued. Thus the oximeter led to the discovery that a marked rise of arterial oxygen saturation could be obtained in this patient by the relatively low inspired oxygen concentrations obtained by nasal catheter; this resulted in the institution of a practical and effective method of treatment.

One rather unusual reaction to oxygen therapy was encountered which we believe is worth while reporting. Case 27, a 58 year old male with emphysema and chronic bronchitis, was admitted to the hospital acutely ill, with extreme cyanosis; temperature 100.2°, dyspnea and orthopnea. X-ray of his chest revealed an extensive bilateral bronchopneumonia in addition to the preexisting pulmonary disease. He was conscious, but slightly disoriented on admission. Oxygen therapy was started coincident with the oximeter run. After 5 minutes of breathing 90 to 97% oxygen, the patient became deeply comatose. His blood pressure rose to 180/100 from a preoxygen level of 130/70. He showed a 30% oximeter rise. When oxygen was stopped, he regained consciousness and his blood pressure fell to its admission level. This series of events could be repeated at will. With nasal oxygen at 7 liters a minute, his oxygen saturation rose approximately 20% and he did not become comatose. Consequently, it was decided to use nasal oxygen for treatment instead of a B. L. B. mask. With massive antibiotic therapy and nasal oxygen, he made a rapid recovery. After resolution of his bronchopneumonia, as judged by both X-ray and

TABLE 2. ACUTE CARDIAC INFARCTION

	Diagnosis	Electrocardiogram	Temperature	Pulse	Respirations	Blood Pressure	Pulmonary Congestion*	Cyanosis†	Oximeter response to inhalation O_2 90–97%		Result
1) J. Lev, white male, 70 yrs.	Ac. card. infarct.	Ac. post. lat. infarct.	99²	90	20	134/76	+	+	7½%		Discharged impr.
2) S. Ang, white male, 57 yrs.	Ac. card. infarct.	Ac. post. lat. infarct.	97	60	16	90/60	0	+	9%	40–50% 6%	Discharged impr.
3) L. Str, white male, 76 yrs.	Ac. card. infarct.	Rec. post. infarct.		120	Cheyne Stokes	90/70	++	0	3½%		Died. Recent and old myoc. infarct.
4) O. Fuh, white male,	Ac. card. infarct.	Ac. ant. infarct.		134	28	147/84	++	++	9½%	40–50% 5%	Died. Necropsy refused.
5) J. Fink, white male, 70 yrs.	Ac. card. infarct.	No evidence recent damage		135	26	90/70	++++	+++	10%	80% O_2 10%	Died. Recent big myoc. infarct.
6) M. Mer, white female, 64 yrs.	Ac. card. infarct.	Suggestive but not diagnostic ac. infarct.	98°	66	20	155/90	+	0	7%	40–50% 4%	Discharged. Further symptoms and E.C.G. changes.
7) B. Bus, white male, 57 yrs.	Ac. card. infarct.	Ac. ant. infarct.		120 fibrillating	18	118/70	+	?	2½%		Discharged impr.
8) J. Fini, white male, 58 yrs.	Ac. card. infarct.	Ext. ant. infarct.		116	24	90/80	0	++	13%	80% O_2 10%	Died. Massive card. infarct.
9) H. Kam, white male, 50 yrs.	Ac. card. infarct.	Ac. ant. infarct.	100	104	20	120/70	+	+	8%		Discharged impr.
10) M. Lis, white male, 62 yrs.	Ac. card. infarct.	Ac. ant. myoc. infarct.	99	100	40	110/80	+++	++	12%	40–50% 7%	Died. Necropsy refused
11) B. Sue, white male, 58 yrs.	Ac. card. infarct.	Ac. ant. lat. myoc. infarct.	98°	...	16	126/80	0	+	6½%		Discharged impr.
12) J. Gol, white male, 68 yrs.	Ac. card. infarct.	Ac. myoc. infarct.		80	26	160/80	0	0	4%		Discharged impr.

* *Pulmonary Congestion* + = few basal râles.
++ = moist basal râles
+++ = râles over lower ½ lung fields
++++ = râles over entire lung fields

† Cyanosis graded + to ++++ on basis of inspection only.

clinical signs, a final oximeter run revealed a response of 12½%. He was still slightly cyanotic as he had been on examination one year previously. Such unusual reactions to oxygen therapy have been described in individuals with chronic anoxemia. These patients are thought to develop a tolerance to oxygen lack by means of changes in the cellular metabolism of their cerebral tissues. Thereafter a sudden increase in arterial oxygen tension may give rise to such symptoms of central nervous system disturbance as somnolence, semi-coma or coma which may last for several days.[1b]

An oximeter response which is significantly greater than the normal may be accepted as evidence that anoxemia is present. However, the converse is not true—a normal oximeter response does not rule out the presence of anoxemia. For instance, a lesion, in which blood enters the left side of the heart without first coming into contact with aerated lung, will produce anoxemia, which will not show a striking response to the inhalation of oxygen. We have observed this failure to respond in a very cyanotic child with the Tetralogy of Fallot. Arterial puncture revealed an arterial oxygen saturation of 53% while breathing room air. Oxygen inhalation of 5 minutes' duration gave a rise of only 5% in the oximeter reading. Another subject with an undiagnosed type of cyanotic congenital heart disease showed only a 6% response to oxygen therapy despite deep cyanosis.

Stagnant anoxemia due to slow circulation, in which blood leaves the heart with a normal oxygen saturation, but passes slowly through the capillary bed and returns to the heart with a very low saturation, theoretically would not show a marked response to oxygen inhalation. This might explain why the responses seen in acute cardiac infarction were relatively small.

We do not believe that a small or "normal" oximeter response necessarily signifies that oxygen therapy is useless if other indications for it exist. In such critical situations as severe myocardial infarction, even a slight increase in the oxygen available to the damaged tissues may be beneficial. When such a patient is given a high concentration of oxygen to breathe, a certain quantity of oxygen is dissolved physically in the plasma in addition to the measurable increase in oxyhemoglobin. The sum represents a substantial increase in the oxygen available for utilization.[2] However, a patient with a small oximeter response is probably less likely to derive benefit from oxygen therapy than a patient with a great response.

The studies reported in this paper indicate that many patients with disease of the heart, lungs, or both, show an abnormally high oximeter response. In general, those with cardiac infarction showed the smallest oximeter response; the patients with congestive failure, small to moderate response; those with pulmonary disease varying response. The most striking results were seen in patients with a combination of pulmonary and cardiac disease. Thus the diagnosis of the pathological process underlying the anoxemic state may give some hint as to the probable response to oxygen. However, there are many individual variations.

In an attempt to improve our ability to predict the response in any given individual we have tried to correlate various clinical signs with the observed response in these patients:

(a) *Cyanosis:* In the groups with pulmonary edema, extensive primary pulmonary disease, and in the mixed group, there was a fairly good correlation between the degree of cyanosis and degree of response. However, cyanosis, except in marked degree, is difficult to evaluate.[3] Patient 26 was thought to be definitely cyanotic by

TABLE 3. CONGESTIVE HEART FAILURE

	Diagnosis	Temperature	Pulse	Respirations	Blood pressure.	*Pul. Congest.**	*Cyanosis†*	*Oximeter response to inhalation O_2 90–97% Varying %*		*Result*
13) A. Med, white male, 56 yrs.	Hypertens. cardiovasc. dis. Pul. edema.	98	90	22	172/120	++	++	7%		Discharged impr.
14) S. Sny, white male, 65 yrs.	Arterioscler. heart dis., congest. failure.	98°	84	28	110/70	++	++	22%		Died. Myoc. ischemia & scarring. Pul. congest.
15) W. Bro, white male, 24 yrs.	Rheum. valvulitis. Congest. failure	98°	66	22	108/80	0	++	10½%		Discharged unimpr.
16) M. Pap, white female, 52 yrs.	Rheum. ht. dis. Mitral sten., fibrillation, congest. failure.	98	100 fibrillating	40		Hydropericr. Partial collapse lt. lower lobe. No râles.	++	13%* *Pt. tolerated mask poorly, result not satisfactory	40–50% 13%	Died: Hydropericard. card. very dilat., mitral stenosis, atelectasis lt. lower lobe.
17) S. Sch, white male, 61 yrs.	Old myoc. infarct., ventric. aneurysm. Chronic congest. failure moderate.	98°	84	20	130/70	+	+++	14%	40–50% 8%	Discharged unimpr.
18) H. She, white male, 40 yrs.	?Mitral sten., hepato-splenomeg., ankle edema, dysp. on exertion.	98°	64	20	102/84	0	0	5%		Died suddenly. Necropsy: mitral sten., card. dilat., pul. congestion.
19) J. Fai, white female, 60 yrs.	Hypertensive, arteriosclerotic ht. dis. Diab. mell. Congest. failure, mild	98°	88	20	230/110	+	+	7%	80% 6%	Discharged unimpr.
20) J. Hav, white male, 68 yrs.	Old myoc. infarct. Hypertensive cardiovasc. dis. Ac. pul. edema		120	22	220/140	++++ and pleural effusion rt. base	++	7%	80% 6%	Discharged impr.
21) C. Del, white male, 62 yrs.	Hypertensive cardiovasc. dis. Pul. edema mod. severe		120	26	160/100	++++	+	7%		Discharged impr.
22) L. Por, white male, 45 yrs.	Card. hypert. and congest. failure, etiology unknown.		99	29	115/90	++	++	14%		Died: Mult. old myoc. infarct., card. dilat. pul. congest.

* *Pulmonary Congestion* + = few basal râles.
++ = moist basal râles
+++ = râles over lower ½ lung fields
++++ = râles over entire lung fields
Cyanosis graded + to ++++ on basis of inspection only.

two of the authors. Yet he showed only a 6% response to 97% oxygen and his arterial oxygen saturation while breathing room air was found to be 94.3% by direct measurement. Conversely Patient 35, in whom cyanosis was regarded as mild, showed a very marked response (22%).

(b) *Pulmonary congestion:* There was no correlation between the oximeter response and the presence of a few pulmonary râles, but frank pulmonary edema was always associated with an increased response, though in some cases the increased response was minimal (Cases 13, 20 and 21).

(c) There was no correlation between blood pressure and the oximeter response except in a few patients with myocardial infarction and in Case 27 (see above).

(d) The Decholin arm-tongue circulation time was determined in a total of 18 patients. It was found to be prolonged in 7 cardiac patients, normal in 7 out of 8 pulmonary patients, and prolonged in 3 of the mixed group. It was of no obvious value in predicting the oximeter response.

(e) Pulse rate was markedly lowered in only 6 patients during the test (Nos, 9, 10, 31, 32, 33, 35). Respiration was significantly lowered in two (Nos. 16, 30). Therefore, these two signs were not frequently enough altered to be reliable indicators. However, it must be emphasized that the period covered by each test was brief and more significant alteration, especially in pulse rate, might have been noted had the test period been longer.

Thus cyanosis and pulmonary edema when present were usually associated with a significant increase in oximeter response. In their absence, no other signs proved reliable for purposes of prediction.

The value of oxygen therapy to prevent anoxemia in anaesthesia, postoperatively and in elderly individuals with pulmonary disease, is well established. In such cases the oximeter may be of value in detecting small degrees of anoxemia, although ideally oxygen therapy should be instituted prior to the development of anoxemia.

The oximeter may be used in negroes, but preliminary tests suggest that the magnitude of the change in the oximeter reading is less than the actual change in arterial saturation.

Summary. (1) Changes in arterial oxygen saturation were measured by means of the Millikan Oximeter in 10 "normal" subjects and 36 patients with cardiac and, or, pulmonary disease (a) breathing room air and (b) breathing 90 to 97% oxygen.

(2) The normal "oximeter response" which we observed as a result of the subject changing from room air to 90 to 97% oxygen was 5% or less.

(3) Patients suffering with a combination of both pulmonary and cardiac disease showed the most marked oximeter response to oxygen therapy. Those with extensive pulmonary disease, or pulmonary edema secondary to cardiac failure, showed moderate response. Patients with acute cardiac infarction showed relatively small responses, although the majority (75%) were above the normal range.

(4) Some patients show remarkable oximeter responses to relatively low inspired oxygen concentrations.

(5) There are certain clinical factors (type of disease, presence of pulmonary congestion, cyanosis) which are of some help in predicting and in evaluating the results of oxygen therapy. However, in many instances the results of oxygen inhalation cannot be predicted, nor can they, as a rule, be accurately evaluated by ordinary clinical methods. The oximeter permits the evaluation of results; it has not helped much in teaching us to predict the results.

TABLE 4. PULMONARY DISEASE

	Diagnosis	Temperature	Pulse	Respirations	Blood pressure	Cyanosis†	Oximeter response to inhalation O_2 90–97%	Oximeter response to inhalation O_2 Varing %	Result
23) H. Kre, white male, 62 yrs.	Silicosis upper 2/3 both lung fields. Emphysema bases. Morning sputum. No other symps.	98°	70	20	145/78	0	3%		Discharged. Cond. unchanged
24) J. Has, white male, 37 yrs.	Emphysema, chronic tracheobronchitis. Dyspnea on exertion.	98°	66	28	120/75	0	8½%		Discharged. Cond. unchanged
25) P. Con, white male, 59 yrs.	Emphysema, severe. Dyspnea on exertion	98°	86	26	104/68	+	8%		Discharged. Unimpr.
26) D. Man, white male, 71 yrs.	Emphysema, chr. bronchitis Dyspnea on exertion.	98	80	22	150/85	Considered "definitely cyano."	6% Vanslyke art. oxygen. sat. 94.3%		Discharged. Unchanged.
27) J. Fis, white male, 58 yrs.	Emphysema, severe, chr. bronchitis. Diffuse bilat. br. pn., cond. critical.	100°	105	38	135/70	+ + + +	30% Deep coma on 90–97% oxygen	40–50% 20%	Discharged improved. Oximeter response 12½% on discharge.
28) J. Sig, white male, 60 yrs.	Spontan. pneumothorax 30% collapse rt. lung. Emphysema, ?cystic dis., of lt. base. Cond. critical	98	62	24	135/80	+ + + +	20%	20% with 60% oxygen 15% with 40% oxygen	Discharged, impr. On 3 subsequent admissions during next 12 mon., progressively severe dyspnea on exertion, marked cyanosis, congest. ht. failure (cor. pulmonale).
29) W. Ste, white	Lobar pneum. rt. lower lobe.	First day 104.2	100	28	108/60	+ +	11%		Discharged. Cured.
		10th day 98.6	90	20	150/80	+	9%		
		15th day 98.6	80	20	150/80	0	5%		
30) J. Sch, white male, 69 yrs.	Bronchogenic ca. involving rt. lower lobe.	Day of admission 98.6	96	20	120/70	+	10%		Died. Necropsy. Bronchogenic ca. rt. lower lobe, br. pn., abscesses.
		21 days after admission 2 days prior to death	110.	44		+ +	13%		

* *Pulmonary Congestion*
+ = few basal râles.
+ + = moist basal râles
+ + + = râles over lower ½ lung fields
+ + + + = râles over entire lung fields

† Cyanosis graded + to + + + + on basis of inspection only.

TABLE 5. MIXED GROUP.

	Diagnosis	Temperature	Pulse	Respirations	Blood pressure	Cyanosis†	Oximeter response to inhalations O_2 90–97%	Oximeter response to inhalations O_2 Varying %	Result
31) G. Slo, white female, 38 yrs.	Old rheum. ht. dis., congest. failure ac., severe Diffuse bilat. br. pn., condition critical, severe shock.	Admission 102	140	40	75/50	++++ greyish pallor shock	20%	40–50% 10%	Discharged impr.
		6 days after admission 98°	80	20	110/60	0	3½%		
32) H. Wei, white male, 65 yrs.	Bronchiectasis-old. Congest. cardi. failure mild 1 yr. duration. ?arteriosclerotic ht. dis. Diffuse br. pn. Friedlander's pneum. condition critical.	Admission 102	94	22	112/90	++++	22%		Discharged impr.
		7 days later "cond. essentially unchanged."				++++	28%		
		28 days after admission 98°	100	20	105/65	0	8%		
33) H. Jud, white male, 50 yrs	Luetic aort. aneurysm, recurrent congest. failure. Atelectasis & infection lt. lower lobe lung due to bron. compression.	100	144	21	140/70	+	12%	40–50% 8%	Discharged impr.
34) A. Bry, white male, 45 yrs	Myoc. infarct. recent. Pul. infarct. mult. Condition critical.	Admission 99°	90	26	116/80	+	11½%	40–50% 5½%	Died suddenly 27 days after adm. Necropsy refused.
		11 days after admission 98°	76	18	125/75	0	2½%		
35) J. Kin, white male 52 yrs.	Pul. emphysema & fibrosis. Sec. polycythemia. Hb 121%, r.b.c. 7.0 million.	Admission 98	88	22	128/80	++	23%		Discharged, cond. unchanged
		9 days after admission cond. unchanged				++	24%		
		6 mos. after 1st adm. cond. unchanged.				++	24%		
36) A. Gro, white male, 44 yrs.	Cor. pulmonale. Pul. emphysema & cystic lower lobes Congest. failure severe on adm.	98	92	18	105/75	++++	30–47% varying. Response checked with arterial blood samples. (Oximeter) 45%	(Van Slyke art. O_2) 49% rise *with 100% O_2.* 30–33% *rise with 30% O_2*	Discharged impr. on regimen of nasal O_2 inhalation at night. 11 months after adm. no evidence of congestive failure, oximeter response remains unchanged.

* *Pulmonary Congestion* + = few basal râles.
++ = moist basal râles
+++ = râles over lower ½ lung fields
++++ = râles over entire lung fields

† Cyanosis graded + to ++++ on basis of inspection only.

(6) An oximeter response greater than normal indicates the presence of anoxemia, and signifies that therapeutic benefit may be expected from oxygen therapy, roughly commensurate with the degree of the response. A normal oximeter response does not rule out anoxemia. It suggests that oxygen therapy will probably be less strikingly beneficial. However, a normal oximeter response does not necessarily indicate that no benefit will be obtained from oxygen inhalation.

(7) Thus the oximeter enables the physician at the bedside to determine the effectiveness of oxygen therapy more accurately than by clinical evaluation, and in certain instances permits him to recognize the presence of anoxemia which might otherwise have been overlooked.

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STUDIES ON BLOOD HISTAMINE
PARTITION OF BLOOD HISTAMINE BEFORE AND AFTER CLOTTING IN HEALTH AND DISEASE STATES*

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THE presence in the peripheral blood of a substance having pharmacologic and toxicologic properties indistinguishable from histamine is a matter of considerable interest. That such an H-substance does exist in measurable quantity has been repeatedly demonstrated and Code and Ing[5] have isolated from whole blood what is apparently the crystalline dipicrate salt of histamine itself. The term "blood histamine" will be used throughout this report to denote the active substance responsible for contracting guinea pig ileum when blood has been extracted according to Code's[8] method for determining blood histamine.

Under ordinary circumstances the blood histamine resides in the cellular component of blood, where it exists in bound form and is pharmacologically inactive. The erythrocytes have been demonstrated to have a relative poverty of histamine activity as have by inference the blood lymphocytes, since normal or low values have been found in lymphatic leukemia.[29] The blood platelets in most species studied are also poor in histamine activity but in the rabbit it is possible these elements may contain considerable quantities of histamine.[12,16,31] The myeloid leukocyte, however, contains the majority of the blood histamine in most animals and in man[4,5,6,7,24] and the blood of human patients with myeloid leukemia may possess histamine activity a hundredfold or more greater than that of blood of normal subjects.[6,28]

Under special circumstances, the blood histamine may be liberated from its inactive form in the cells to a free state in the plasma or serum where it is pharmacologically active. Appreciable amounts of free histamine are found in blood plasma after anaphylactic shock in certain species,[9] and trypsin injected intravenously is capable of liberating histamine from blood cells[3] as well as from other tissues.[20] Histamine may pass from cells to plasma in vitro when peptone[30,13] or proteolytic enzymes such as trypsin[10,27,19,3] or papain[21] are added to blood, or when specific antigen is incubated for a short period with sensitized blood.[14,15] Plasma histamine also increases during reactive hyperemia and muscle contraction in man.[2]

It has also been repeatedly stated that histamine release from cells to serum occurs when blood coagulates. Many investigators have noted pharmacologic activity in serum which was not present in plasma. It is not suitable to review here the literature relative to such differences between serum and

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plasma in view of the numerous discussions already available. Suffice it to say that while part of the activity present in serum has been clearly shown to be due to substances other than histamine,[18,32] the latter has none the less been suspected of being partially responsible for the pharmacologic properties observed. Code[4,5] in 1937 found that 69 to 90% of the total blood histamine in rabbits passed from cells to serum when blood was allowed to clot and in a single experiment demonstrated histamine in human serum. The results in rabbits are of course somewhat clouded by the possibility that the platelets of this species may contain appreciable amounts of histamine. Grana and Rocha e Silva[12] have reported confirmation of Code's observations and Selle[25] in an extensive review has stated that histamine liberation from cells is associated with coagulation of blood. Anrep and co-workers[1] could not find histamine in human serum and Reid[18] has recently concluded that in the serum of man (and in certain animal species) the main substance stimulating guinea pig jejunum is not histamine.

It was the purpose of this investigation on human subjects (1) to determine the effect of coagulation on the partition of histamine between cells and serum, and (2) to investigate the blood histamine levels in certain disease states and if possible to correlate the differential leukocyte picture with the level of blood histamine. In connection with the primary objective it was felt that reports of histamine liberation as a phenomenon associated with the coagulation of blood were of considerable interest and worthy of further investigation. There was no obvious explanation as to why the entrapment of leukocytes within a fibrin mesh should result in loss of their histamine unless some biochemical process incident to blood clotting was responsible. The fact that proteolytic, trypsin-type enzymes have been suspected by some[11,26] to play an important rôle in the coagulation of blood and that similar enzymes have been demonstrated as capable of releasing histamine from blood cells to plasma fostered the hope that studies on the partition of histamine after coagulation might give some clue as to the presence or absence of such enzyme activity during clotting.

Methods. In the partition studies, blood was withdrawn without stasis into a clean dry syringe from the antecubital veins of 4 normal adults, one patient with leukocytosis and bladder malignancy, and 2 adults with chronic myelogenous leukemia. In one of the patients with chronic myelogenous leukemia 2 separate determinations were made—one shortly before and one shortly after a course of radiation. Blood was always carefully handled to avoid trauma in so far as possible. Suitable samples of whole blood (never less than 10 cc. in the case of normal individuals) were placed directly and without anticoagulants into trichloroacetic acid. In each instance the remainder of the blood obtained was placed in a clean glass flask containing glass beads and defibrinated by gentle rotation of the flask. The clotted defibrinated blood was then transferred, beads, fibrin and all, to a clean tube and centrifuged at 2500 to 3000 r.p.m. for 8 to 10 minutes. Suitable serum samples were obtained by pipetting off the serum down to 1-2 cc. above the cell-serum interphase. These serum samples were likewise placed in trichloroacetic acid and treated in a manner identical to that employed with whole blood. The amount of serum available for extraction was never less than 7 cc. in the case of normal individuals, was 3.5 and 7.5 cc. respectively in the 3 determinations made on the leukemic blood and 5 cc. in the determination made on the patient with bladder malignancy and leukocytosis. In the leukemic patients, a well defined white cell layer separating erythrocytes from serum was readily apparent when the clotted defibrinated blood was centrifuged. In all determinations made on these patients additional samples were taken from this leukocyte rich layer after defibrination and centrifuging. It was possible to determine in this way if the leukocytes still retained their histamine after clotting. In all instances the cells, serum and clot were allowed to remain in contact approximately 25 to 30 minutes from the time clotting began.

In every experiment except one, total and differential leukocyte counts were made on each whole blood specimen assayed. Total leukocyte counts were made on each serum sample with one exception, and on the leukocyte rich samples obtained from leukemic blood after defibrination.

In an associated group of studies, whole blood histamine values were obtained from subjects with a wide variety of disease states. In such studies 5 to 10 cc. of whole blood were placed directly in trichloroacetic acid without the addition of anticoagulants. All specimens in each experiment were extracted by Code's modification[8] of the method of Barsoum and Gaddum and assayed on atropinized terminal guinea pig ileum suspended in 2½ to 3 cc. of Tyrode's solution. Serum samples were extracted in the same manner as whole blood in order to be certain as nearly as possible that the activity assayed was due entirely to histamine.

it is realized that if histamine were liberated nearly quantitatively from cells to serum, each cc. of serum from the normal individuals should contain the amount of histamine originally present in slightly less than 2 cc. of whole blood. While the results are sufficiently definite in normal subjects, the determinations are given added significance by the enormous differences in serum and whole blood histamine observed in individuals with myelogenous leukemia. In the latter cases, it was also possible to demonstrate that the myeloid leukocytes still contained large amounts of histamine *after* defibrination. It appears reasonable to state that in man there is little or no libera-

TABLE I — HISTAMINE DETERMINATION IN HUMAN SUBJECTS ON WHOLE BLOOD BEFORE CLOTTING AND ON SERUM AFTER CLOTTING AND DEFIBRINATION

Patient	Age	Diagnosis	Sample	Leukocyte counts per cu. mm.	Histamine in gamma per cc.
W.N.V.	29	Normal	Whole Blood		0.079
			Serum		0.015
R.P.	32	Normal	Whole Blood	6,250	0.057
			Serum	200	0.013
W.S.A.	27	Normal	Whole Blood	6,550	0.070
			Serum	50	0.012
C.G.C.	25	Normal	Whole Blood	6,450	0.09
			Serum	50	0.01
A.K.	60	Cancer of bladder Bladder infection	Whole Blood	20,550	0.088
			Serum	50	0.016
I. R.*	34	Chronic Myeloid Leukemia	Whole Blood	128,000	8.00
			Serum	0	0.15
			Leukocyte-rich layer ‡	258,000	7.10
J.R.†	34	Chronic Myeloid Leukemia	Whole Blood	36,000	2.12
			Serum	100	0.10
			Leukocyte-rich layer ‡	109,500	5.55
W.C.G.	36	Chronic Myeloid Leukemia	Whole Blood	164,000	1.32
			Serum	150	0.066
			Leukocyte-rich layer ‡	320,000	3.57

KEY: * before course of radiation.
† after course of radiation.
‡ from upper cellular layer of defibrinated blood after centrifuging.

EFFECT OF CLOTTING ON PARTITION OF HISTAMINE BETWEEN CELLULAR AND FLUID COMPONENTS OF HUMAN BLOOD. The data are summarized in Table 1. All histamine values are in gammas of histamine base per cubic centimeter of sample.

It is seen that in every instance only a very small fraction of the original cellular histamine has appeared in the serum after coagulation. The differential between whole blood and serum histamine is even more striking when

tion of histamine occurring as a result of coagulation of blood per se, and that important pharmacological activity due to histamine in serum obtained within 30 minutes of clotting under the conditions of these experiments does not exist. The presence of relatively enormous amounts of histamine in the white cell layer of centrifuged defibrinated leukemic blood supports the now generally accepted view that in man the majority of histamine is found in the myeloid leukocyte. Since clotting has

occurred, platelets cannot be said to be an important element in this white cell layer.

The failure to observe histamine release from cells to serum during coagulation does not support the concept that a proteolytic enzyme of the trypsin type is an important factor in coagulation of human blood. Trypsin and certain other proteolytic enzymes, it is now well established, have the ability to liberate histamine from cells.[3,10,19,27] The data do not exclude the possibility that some proteolytic enzyme not capable of producing histamine release is concerned in coagulation of human blood. Indeed they do not preclude that an amount of trypsin or trypsin-like enzyme large enough to play a rôle in coagulation was present, but that this was not in sufficient concentration to produce histamine release. These possible quantitative considerations must await further investigation. The relationship of the amount of trypsin necessary to promote coagulation on the one hand and to release histamine on the other may serve as a convenient clue to its presence or absence in the coagulation mechanism.

Studies on Blood Histamine Levels in Human Patients. Survey determinations have been made on patients with the following syndromes or diseases: chronic and acute myelogenous leukemia, chronic lymphogenous leukemia, reticulum cell sarcoma, leukopenia of undetermined eitology, multiple myeloma, idiopathic thrombopenic purpura, Mikulicz syndrome, Raynaud's disease, idiopathic hypoprothrombinemia, trichinosis, pernicious anemia in relapse and after therapy, idiopathic nonthrombopenic purpura, carcinoma and infection of the bladder, Hodgkin's disease, Addison's disease, pneumococcal pneumonia, and macrocytic anemia with eosinophilia of undetermined etiology. In all instances total and differential leukocyte counts were made at approximately the time blood was withdrawn for histamine studies. No attempt was made to investigate patients with allergic disease since reports are available on this group of individuals.[17,22,23]

While most normal individuals have blood histamine levels below .08 gamma histamine base per cc. of whole blood, we have considered only those patients with levels in excess of 0.10 gamma per cc. to have grossly abnormal values. By such a criterion, with the exception of patients with myeloid leukemia, only one individual studied had an abnormally high blood histamine level. This individual had a macrocytic anemia, leukocytosis of 23,600 per cu. mm. with eosinophilia, and the diagnosis was not clear. The blood histamine level in this instance was 0.18 gamma per cc. of whole blood. The patient ultimately died outside the hospital and no autopsy was performed.

It is clear that there is no close correlation between total or differential leukocyte count and the blood histamine. It was true in our series that individuals with very low numbers of granulocytes often had very low blood histamine values, but this is difficult to evaluate since normal subjects may also have markedly low histamine levels at times. However, while subjects with higher granulocyte counts tended to have somewhat higher histamine values, there was by no means a proportionate increase. Thus the blood histamine of a patient with carcinoma and infection of the bladder who had a total leukocyte count per cu. mm. of 20,500 with 80% granulocytes was 0.088 gamma per cc. The blood of a patient with 15,800 leukocytes per cu. mm. and 85% granulocytes contained but 0.05 gamma per cc., less than that of some normal subjects with normal counts. Nor was there close correlation found with any particular member of the granulocyte series. For example, one

patient with trichinosis and an absolute eosinophilia of 6300 per cu. mm. had a blood histamine level of but 0.03 gamma per cc. of blood while another individual with Hodgkin's disease and 5300 eosinophils per cu. mm. exhibited a level per cc. of 0.10 gamma. The patient with the elevated blood histamine of 0.18 gamma per cc. also had an absolute eosinophilia of 6500 per cu. mm. This lack of close correlation with total or differential leukocyte counts becomes even more apparent in patients with chronic myelogenous leukemia where histamine values of tremendous magnitude were obtained. Table 2 shows the findings in this group.

TABLE 2 — TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS AND BLOOD HISTAMINE VALUES IN HUMAN SUBJECTS WITH CHRONIC MYELOGINOUS LEUKEMIA

Patient	Date	Total WBC per cu. mm.	Bas.	Eos.	Blast	Myelo.	Juv.	Stabs.	Seg.	Lymphs.	Monos.	Other	Histamine base in gamma per cc. whole blood
W.C.G.*	7- 2-46	199,500	2.5	2.0	0.5	21.5	17.0	33.0	33.0	2.0	0.0	1.0	2.5
W.C.G.*	10-21-46	164,000	2.0	1.0	0.0	18.0	13.5	28.0	35.0	2.0	0.0	0.5	1.32
J.R.* before x-ray	9-17-46	128,000	5.5	2.0	2.0	18.0	21.5	32.5	14.0	3.5	0.0	1.0	8.0
J.R.* after x-ray	9-30-46	36,000	2.0	2.5	0.0	13.5							
F.T.	11-12-46	177,000	2.5	4.0	1.0	24.5	5.5	26.0	43.5	4.5	0.0	2.5	2.12
							14.0	30.0	31.5	2.0	0.0	0.5	3.75

* Same patient where initials are the same.

It is readily apparent that differences in differential cell types or total leukocyte counts do not permit any conclusions as to which members of the granulocyte series are richest in histamine content. It is of interest that the blood histamine level of J. R. fell almost proportionately with the leukocyte count after roentgen radiation therapy. In addition to the above, one patient with acute myelogenous leukemia was studied. The total leukocyte count was only 9700 per cu. mm. with 12% blast cells. The blood histamine level was 0.10 gamma per cc. of blood—at upper limits of normal or perhaps slightly above. In a single case of chronic lymphatic leukemia with 475,000 cells per cu. mm. the blood histamine was low—0.025 gamma per cc. of whole blood.

It is also apparent that mere increase in numbers of cells cannot explain the tremendous amount of blood histamine in some cases of myelogenous leukemia. Thus, computing from normal values, the total cell count in J. R. and in F. T. cannot adequately explain the marked increase above normal of the blood histamine. The individual cells must contain much more histamine than normal cells, but whether this is limited to certain stages of cell development or is a general phenomenon cannot be ascertained from our data.

It is interesting to speculate on the significance of the histamine content of the myeloid leukocyte both in normal individuals and in patients with myelogenous leukemia. Little is known of the physiologic functions, if any, of histamine within the body. However, there is probably sufficient histamine within the myeloid leukocytes of many normal individuals to produce significant effects if any large portion of it were suddenly liberated.[14] In anaphylactic reactions histamine liberated from blood cells may be added to that liberated from other tissues. The extremely large amounts of blood histamine found in patients with myelogenous leukemia, if liberated rapidly, could most certainly result in profound clinical symptoms. In view of the probability that there is a rapid turnover of leukemic leukocytes within the body, one can but wonder what effect the liberation of histamine may have on the economy of these patients. In the case of normal individuals with localized pyogenic infection it is

possible that the cardinal signs of inflammation may be partly due to the breakdown of large numbers of myeloid leukocytes with local liberation of histamine. Certainly, the so-called "cold abscess" in which the non-histamine containing mononuclear is the predominant cell type involved presents far different clinical manifestations than the pyogenic abscess with its predominantly granulocytic exudate.

Summary. Data are presented on the partition of blood histamine before and after clotting and on the correlation of blood histamine levels with the blood leukocyte picture in health and disease states. The data support the now generally accepted view that most of the blood histamine in man is found in the myeloid leukocyte. They show that there is little if any transfer of histamine from cells to serum when human blood is allowed to clot. Tremendous elevations in blood histamine were found in patients with chronic myelogenous leukemia, but no close correlation was obtained between the level of blood histamine and the total or differential leukocyte count. The possible significance of the presence of appreciable amounts of histamine within the myeloid leukocyte is discussed.

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THE INTERRELATIONSHIP OF HODGKIN'S DISEASE AND OTHER LYMPHATIC TUMORS†

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THE cellular structure of lymphatic tumors is extremely labile, and transition from one apparently distinct type to another is frequently observed. This is not surprising, when one appreciates that all cellular components of lymphatic tissue are derived from the same mesenchymal stem cells. Attempts to subdivide these interrelated tumors on the basis of rigid histologic criteria have resulted in a confused nomenclature which serves only to cloud the facts. Radiologists and clinicians, even many experienced pathologists, prefer to regard the subgroups as separate neoplastic entities. Thus, a differential diagnosis between Hodgkin's disease and reticulum cell sarcoma, or between lymphosarcoma and chronic lymphatic leukemia, would seem to make a great deal of difference; actually it makes little or none. They are all malignant mesenchymal tumors which vary only in degree and type of differentiation.

The views that we are presenting are not new. As early as 1906 Gibbons regarded Hodgkin's disease as a variant of lymphosarcoma, and the following year Coley suggested that the term "Hodgkin's disease" be dropped in favor of "lymphosarcomatosis." Ginsburg (1934) came to the conclusion that "biologically, Hodgkin's disease varies in no fundamental characteristic from lymphosarcoma. Whatever variations it may present at times are merely variations that one would expect to find in any disease affecting different individuals under different constitutional and environmental conditions."

In 1913 Oliver added "endothelioma" (reticulum cell sarcoma) to the group, and Warren and Picena (1941) clearly demonstrated the steps which linked reticulum cell sarcoma with lymphosarcoma, although they omitted Hodgkin's disease which they considered "a more complicated process and still controversial." Earlier, however, Callender (1934) implied that reticulum cell sarcoma and the sarcomatous form of Hodgkin's disease were closely allied. The relationship between Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, was shown by Herbut, Miller, and Erf (1945), who described 6 cases "that at one time during the lives of the patients were diagnosed Hodgkin's disease and at another time

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as lymphosarcoma, and that at autopsy showed various combinations of Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma." They considered "the three diseases as arising from a common stem cell—the reticulum cell—and then differentiating in one direction or another according to the amount and type of stimulation."

Mallory (1914) proposed the term "malignant lymphoblastoma" to include lymphosarcoma, lymphatic leukemia, and Hodgkin's disease; two years later Warfield and Kristjanson described a case which featured all three of these variants, a patient with a typical lymphosarcoma in whom a lymphatic leukemic blood picture developed and whose axillary lymph nodes, removed shortly before death, presented the histologic appearances of Hodgkin's disease. Richter (1928) observed a case of "generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia," while Gittins and Hawksley (1933) reported the coexistence in a child of reticulum cell sarcoma and monocytic leukemia.

Warthin (1931) stated "that Hodgkin's disease is a neoplasm and related genetically to the lymphoblastomas, of which both the aleukemic and leukemic forms are identical pathologically; and that mycosis fungoides is likewise a neoplasm belonging to the same generic group. The essential difference between these different clinical forms consists in different degrees of dedifferentiation and entdifferentiation, and the organ or tissue primarily involved. Transition forms exist between all of these groups, and one type may be transformed into another." Warthin's inclusion of mycosis fungoides in the group was supported by the papers of Wile and Stiles (1935) and MacCormac (1941), each of which contained the description of a mutation from this condition to Hodgkin's disease.

We found only one reference to fibrosarcoma as an associated variant among the lymphomas, a situation that we encountered 8 times in our series. Fraser and Meckie (1933) described their Case 10 as having had a biopsy performed which was typical of Hodgkin's disease. At autopsy "in some parts the histological appearances were unequivocally those of Hodgkin's disease, but in other parts the tissue was almost wholly composed of immature fibroblasts, with here and there a distorted though plainly recognizable Dorothy Reed cell."

The most labile of all lymphatic tumors is the follicular lymphoblastoma which rarely retains its identity throughout the course of the disease, but at some unpredictable time undergoes transition to lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia, Hodgkin's disease, or combinations thereof. Symmers (1938) (1941) (1942) (1948) described such transformations. Recently, under the title "Manifold Manifestations of Reticulo-Endothelial Disease," Tedeschi and Carnicelli reported a case showing first a "cervical granuloma which disclosed the characteristic pattern of Hodgkin's disease; then acute hemolytic anemia, which successfully responded to splenectomy, and last a recurrence of the cervical granuloma in association with giant follicular lymphadenopathy."

Material. For some years we have been aware of the fluidity existing among tumors of lymphatic tissue. An assignment to examine and render a report on all lymphatic and hemopoietic tissues submitted to the Army Institute of Pathology during the recent war offered a unique opportunity to study this problem in detail. The number of cases was statistically significant, and in many the course of the disease could be followed through the medium of one or more biopsies to the autopsy. Records in most instances were good, and the tissue samples adequate.

The study was centered principally around Hodgkin's disease. Any case in which this diagnosis was not completely acceptable on the basis of either biopsy or autopsy specimens was discarded. The final *Hodgkin's material*, comprised 700 cases as follows:

Autopsy Series:	Cases
With no biopsy	62
With 1 biopsy	113
With 2 biopsies	21
With 3 biopsies	4
	200
Biopsy Series:	
One biopsy	431
Two biopsies	60
Three biopsies	9
	500

The serial biopsies served to augment the biopsy-autopsy material in the study of transitions from one variant to another, while the single biopsies proved valuable in determining the incidence of several histologic patterns in the same lymph node.

An additional series of 600 cases contained *lymphomas apart from Hodgkin's disease* (follicular lymphoblastoma, lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia, monocytic leukemia). This group included cases displaying transitions and combinations among themselves, and furnished data with which to complete our scheme of interrelationship (Fig. 1).

Careful note was made of treatment given the patients, especially with radiant energy. A significantly large group had received no treatment and could be used as a control. Radiotherapy apparently had no influence either in initiating or deterring transitions. Naturally occurring fibrosis sometimes exceeded that observed in heavily irradiated patients, and little or no fibrous reaction was apparent in the tumors of others who had received large doses of Roentgen-rays.

TERMINOLOGY AND HISTOLOGIC CRITERIA. We grouped our cases of *Hodgkin's disease* according to the histologic classification of Jackson and Parker (paragranuloma, granuloma, sarcoma) on the basis of the predominating microscopic pattern, even though the picture was a mixed one in many instances. Thus we could include considerable changes in cellular structure within this single disease category.

Hodgkin's paragranuloma is characterized by a partially to completely effaced nodal pattern, with small lymphocytes predominating, along with a scattering of plasmacytes, reticulum cells, and Reed-Sternberg cells (Plates 1B, 2A, 3A, 8A). *Hodgkin's granuloma* is the oldtime textbook picture that needs no further elaboration (Plates 1B, 2B & D, 3B, 4D, 5A, 6A, 7A, 10B & C). We did not find any fundamental difference between *Hodgkin's sarcoma* and *reticulum cell sarcoma,* and consequently used the terms synonymously in our scheme (Fig. 1), irrespective of the fortuitous occurrence of tumor giant cells that could be regarded as Reed-Sternberg cells. Both reticulum cell and Hodgkin's sarcoma showed variants from an anaplastic, syncytial pattern to a well differentiated reticulum cell structure (Plates 1E, 2D, 3C & D, 5B & C, 6B, 7B, 8D, 10A, 11D).

Follicular lymphoblastoma is a lymphatic tumor, localized or multicentric, in which there is differentiation to follicles, to be distinguished from reactive hyperplasia of follicles, though sometimes with difficulty. Striking numerical (not necessarily dimensional) increase in follicles, distortion of nodal pattern, and absence of phagocytosis within follicular centers serve to distinguish the tumor (Plates 1A, 11B).

Lymphosarcoma denotes tumors made up of relatively uniform round cells which may be small, well differentiated lymphocytes (lymphocytoma) or large, anaplastic lymphocytes (lymphoblastoma) (Plate 8C & E, 11C).

Lymphatic leukemia differs only in being a more generalized neoplasia without striking local tumefaction, with or without the appearance of lymphoid cells in the circulating blood (Plate 11A & C). The same relationship exists between *monocytic leukemia* and *reticulum cell* sarcoma as regards the type of proliferating cell.

These terms are useful, but only to designate the predominating histologic pattern of a lymphoma at the time of a particular examination of tissue and blood.

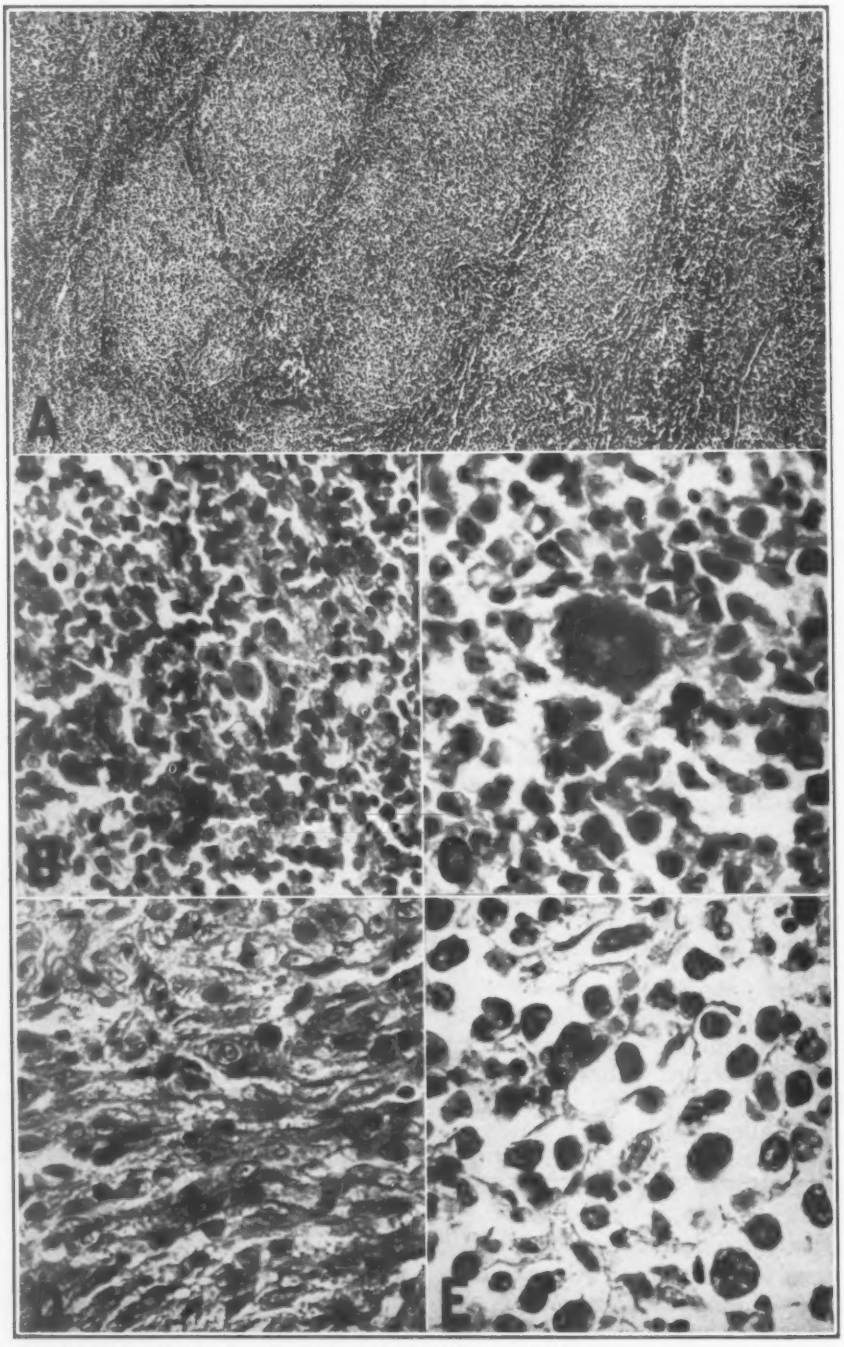

PLATE 1.—White female, 33. Duration 23 months. Radiotherapy 7600 r.

A. 1st biopsy (lymph node): Follicular lymphoblastoma; large, closely packed lymphoid nodules uniformly distributed throughout the node (X32).

B. 2nd biopsy (lymph node): Hodgkin's paragranuloma; small lymphocytes predominate; a Reed-Sternberg cell is seen in the center (X600).

C. 3rd biopsy (lymph node): Hodgkin's granuloma; the dark smudgy cells are eosinophils and the large central cell a Reed-Sternberg form (X600).

D. Autopsy (lymph node): A sarcomatous proliferation of fibroblasts entirely replacing nodal parenchyma (X600).

E. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma, the predominating picture in lesions found at autopsy (X600).

(A.I.P. Acc. 138816. Neg. Nos. 94710, 93009, -008, -012, -013.)

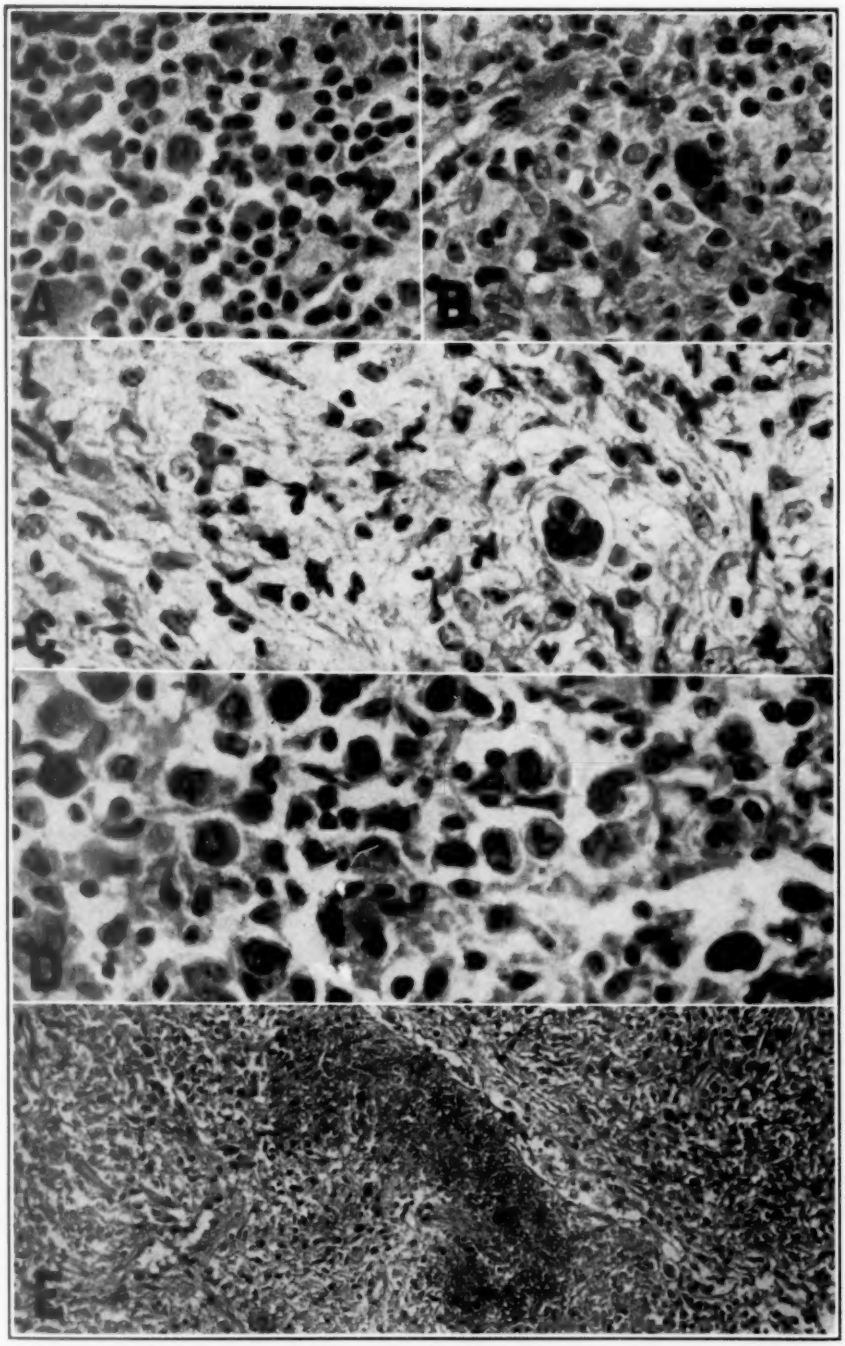

PLATE 2.—Colored male, 23. Duration 13 months. Radiotherapy, none.

A. First biopsy (lymph node): Hodgkin's paragranuloma; a binuclear plasmacyte is seen in the lower right center, an atypical reticulum cell in the upper left center, and a Reed-Sternberg cell in extreme lower left; most other cells are small lymphocytes (X600).

B. First biopsy (lymph node): A small area of same node as A acquiring granulomatous characters, with proliferation of reticulum cells and fibroblasts (X600).

C. Second biopsy (lymph node): Hodgkin's granuloma with marked fibrosis (X600).

D. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma, being the type lesion found in all nodes examined (X600).

E. Autopsy (spleen): Hodgkin's granuloma; very little sarcomatous change was evident in the richly distributed splenic lesions; some granulomatous foci also persisted in the liver (X130).

(A.I.P. Acc. 118663, Neg. Nos. 93018, -019, -020, -021, -022.)

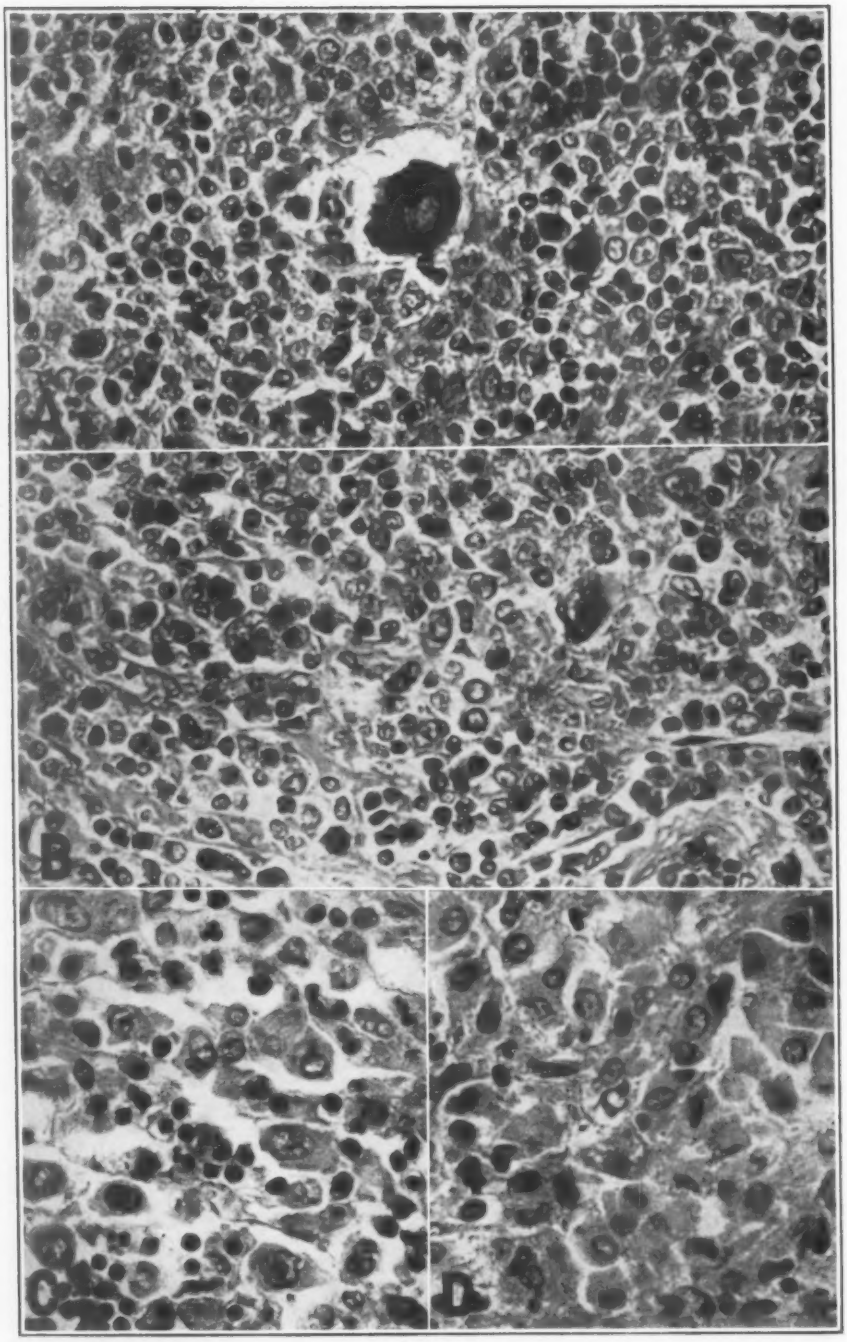

PLATE. 3.—White male, 35. Duration 10 months. Radiotherapy, not stated.

A. 1st biopsy (lymph node): Hodgkin's paragranuloma; proliferation of reticulum cells and a few fibroblasts among the lymphocytes heralds a transition to the granulomatous form; the Reed-Sternberg cell in the center is extraordinarily large (X600).

B. 2nd biopsy (lymph node): Hodgkin's granuloma, most of the lymphocytes have disappeared, and a pronounced eosinophilia is present (X600).

C. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma showing an admixture of large reticulum cell and small lymphocyte components (X600).

D. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma, with a virtually pure reticulum cell proliferation (X600).

(continued on Plate 4)

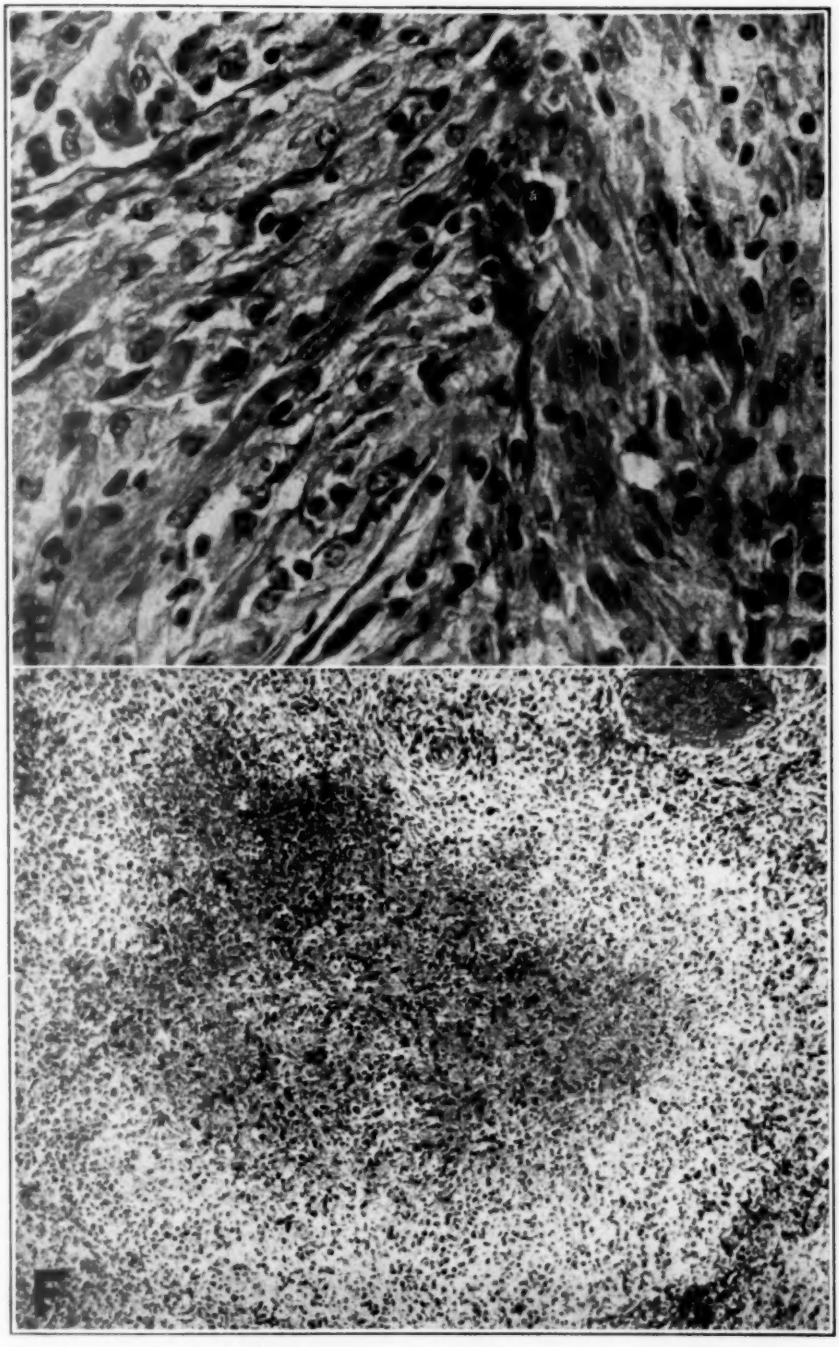

PLATE 4.—Same case illustrated in Plate 3.

E. Autopsy (liver): Fibrosarcoma; interlacing fasciculi and herring-bone sweeps of obviously neoplastic fibroblasts; this type of reaction was limited to the liver (X600).

F. Autopsy (spleen): Hodgkin's granuloma; these large residual granulomatous foci were widely scattered throughout the organ and showed virtually no sarcomatous change (X170).

(A.I.P. Acc. 96380. Neg. Nos. 92965, -966, -969, -970, -972, -973.)

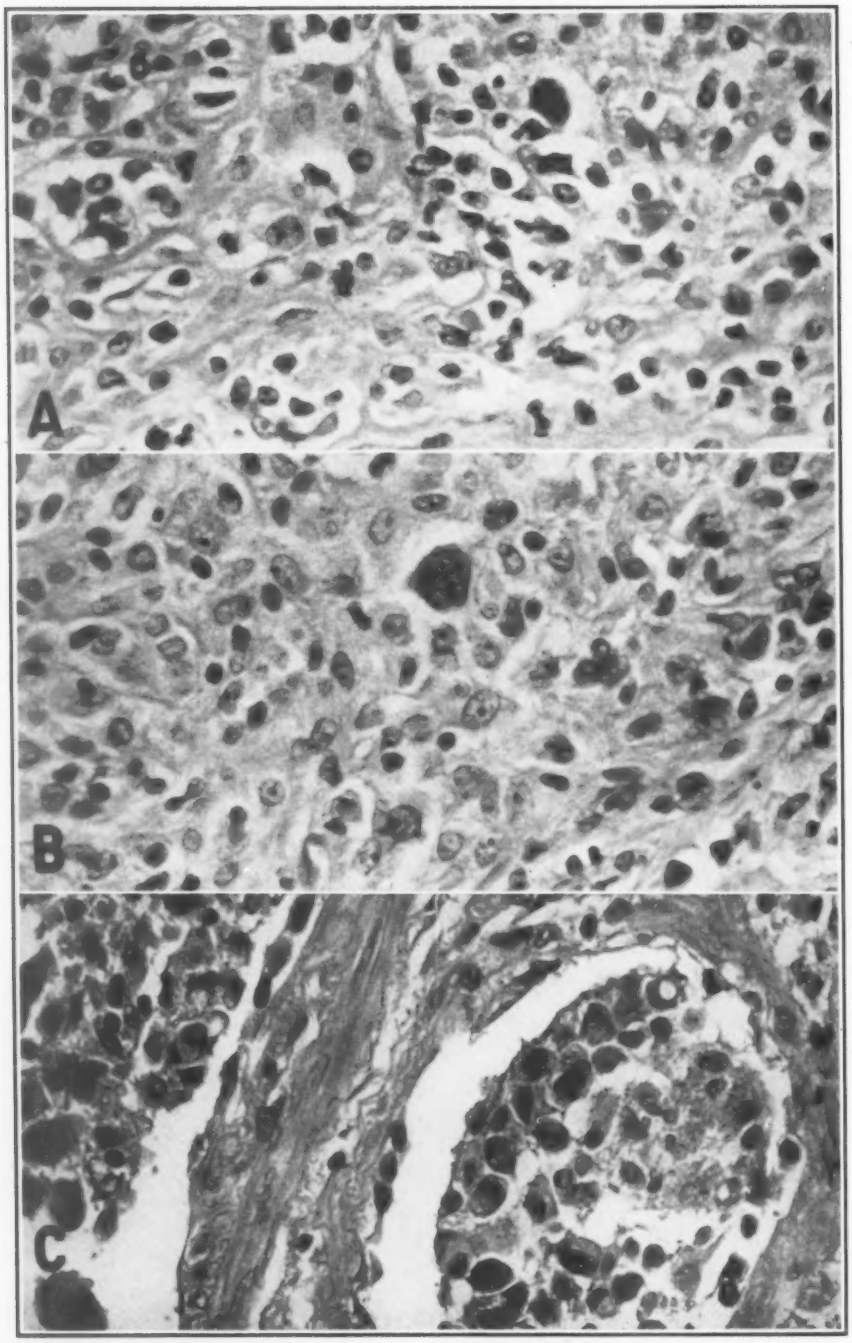

PLATE 5. White male, 29. Duration 5½ months. Radiotherapy 12,800 r.

A. 1st biopsy (lymph node): Hodgkin's granuloma; collagen deposit throughout the node is abundant (X600).

B. 2nd biopsy (lymph node): Stage of transition between Hodgkin's granuloma and sarcoma (X600).

C. Autopsy (perinodal tissue): Hodgkin's (reticulum cell) sarcoma; all granulomatous features have disappeared, and the tumor shows extensive invasion and metastasis via vascular pathways (X600). (A.I.P. Acc. 130157. Neg. Nos. 93023, -024, -025.)

Observations. Cases of Hodgkin's disease were divided according to the (to the) Jackson-Parker classification as in table below.

In Fig. 1 the arrows leading to and from the Hodgkin's disease rectangle, and those contained within it, indicate the transitions actually observed in this series, the heavy lines showing the most common changes and the double-headed arrows the to-and-fro shifts.

A virtually complete alteration in the histologic pattern of the tumor was noted in 39% of the 138 autopsied cases in which biopsies were available, and in 31% of the serial biopsy group (Table 1). Still more striking was the incidence of pure type tumors in only 19 and 23% respectively in these two groups. When only one observation was possible, either of autopsy or biopsy material, unmixed pictures were found in the majority of cases (74 and 71%); this may have represented either an early phase before transition was initiated, or a late one after the pattern was finally established.

Major transitions are listed in Table 2. In both the biopsy-autopsy and sequential biopsy series the most fre-

	Autopsy Series		Biopsy Series		Total	
	No.	%	No.	%	No.	%
Hodgkin's paragranuloma	7	3.5	93	18.6	100	14.3
Hodgkin's granuloma	120	60.	378	75.6	498	71.1
Hodgkin's sarcoma	73	36.5	29	5.8	102	14.6
Total	200		500		700	

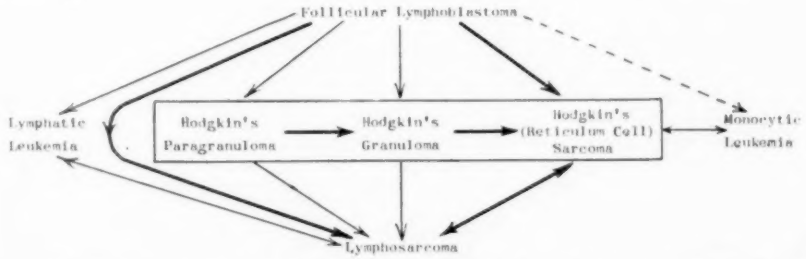

FIG. 1.—This diagram represents transitions actually observed between the several variants of malignant lymphoma, and is not to be construed as indicating genetic sequences. The heavy lines show transitions most frequently found, the lighter lines the uncommon ones. Double-headed arrows signify a change in either direction. The dotted line implies a possible sequence not encountered in our series. Associated fibrosarcomas are not shown here.

TABLE 1.—TRANSITIONS AND COMBINATIONS OF HISTOLOGIC TYPES.

	With Transition		Without Transition		Pure Type		Combined Types		
	No.	%	No.	%	No.	%	No.	%	Cases
	Autopsy Series (200 cases)								
With Biopsy	54	39	84	61	26	19	112	81	138
Without Biopsy	--	--	--	--	45	74	17	26	62
	Biopsy Series (500 cases)								
Sequential Biopsies	21	31	48	69	16	23	53	77	69
Single Biopsy	--	--	--	--	305	71	126	29	431

TABLE 2.—VARIETIES OF MAJOR TRANSITIONS OBSERVED.

	Initial Type	Terminal Type	Cases
Autopsy Series with Biopsy:	Hodgkin's paragranuloma	Hodgkin's granuloma	7
	Hodgkin's paragranuloma	Hodgkin's sarcoma	6 (†)
	Hodgkin's granuloma	Hodgkin's sarcoma	28
	Hodgkin's granuloma	Fibrosarcoma	1
	Hodgkin's sarcoma	Hodgkin's paragranuloma	2 (?) (*)
	Hodgkin's sarcoma	Hodgkin's granuloma	8 (?) (*)
	Follicular lymphoblastoma	Hodgkin's granuloma	1
	Follicular lymphoblastoma	Hodgkin's sarcoma	1
Sequential Biopsy Series:	Hodgkin's paragranuloma	Hodgkin's granuloma	7
	Hodgkin's granuloma	Hodgkin's paragranuloma	1 (?) (*)
	Hodgkin's granuloma	Hodgkin's sarcoma	9
	Hodgkin's sarcoma	Hodgkin's granuloma	2 (?) (*)
	Follicular lymphoblastoma	Hodgkin's paragranuloma	1
	Follicular lymphoblastoma	Hodgkin's sarcoma	1

(†) One of these was a combination of Hodgkin's (reticulum cell) sarcoma and lymphosarcoma, the two types being distinct in separate foci.

(*) It is not clear whether these cases show a reverse transition toward better differentiation, or whether the biopsy merely disclosed a local variant of the major type of lesion observed at autopsy.

TABLE 3.

TYPE LESIONS OBSERVED IN DIFFERENT LYMPH NODES OR ORGANS OF THE SAME INDIVIDUAL AT AUTOPSY (129 cases)

Hodgkin's paragranuloma		X	X			X	X	X			
Hodgkin's granuloma	X	X	X	X	X				X		
Hodgkin's sarcoma	X		X	X	X	X	X	X	X	X	
Lymphosarcoma					X	X					
Fibrosarcoma				X							
Follicular lymphoblastoma								X	X	X	
Number of cases	90	13	13	4	3	2	1	1	1	1	

COMBINATIONS OF TYPE LESIONS(*) OBSERVED IN SINGLE LYMPH NODES (255 cases)

Hodgkin's paragranuloma		X	X	X				X		X		
Hodgkin's granuloma	X	X			X	X	X	X	X		X	
Hodgkin's sarcoma	X			X			X	X	X	X		X
Lymphosarcoma					X				X			
Fibrosarcoma						X	X					
Follicular lymphoblastoma			X							X	X	X
Number of cases	132	101	7	4	2	2	2	1	1	1	1	1

(*) Histologic patterns of significantly large fields which, if viewed alone, would justify the diagnoses as listed.

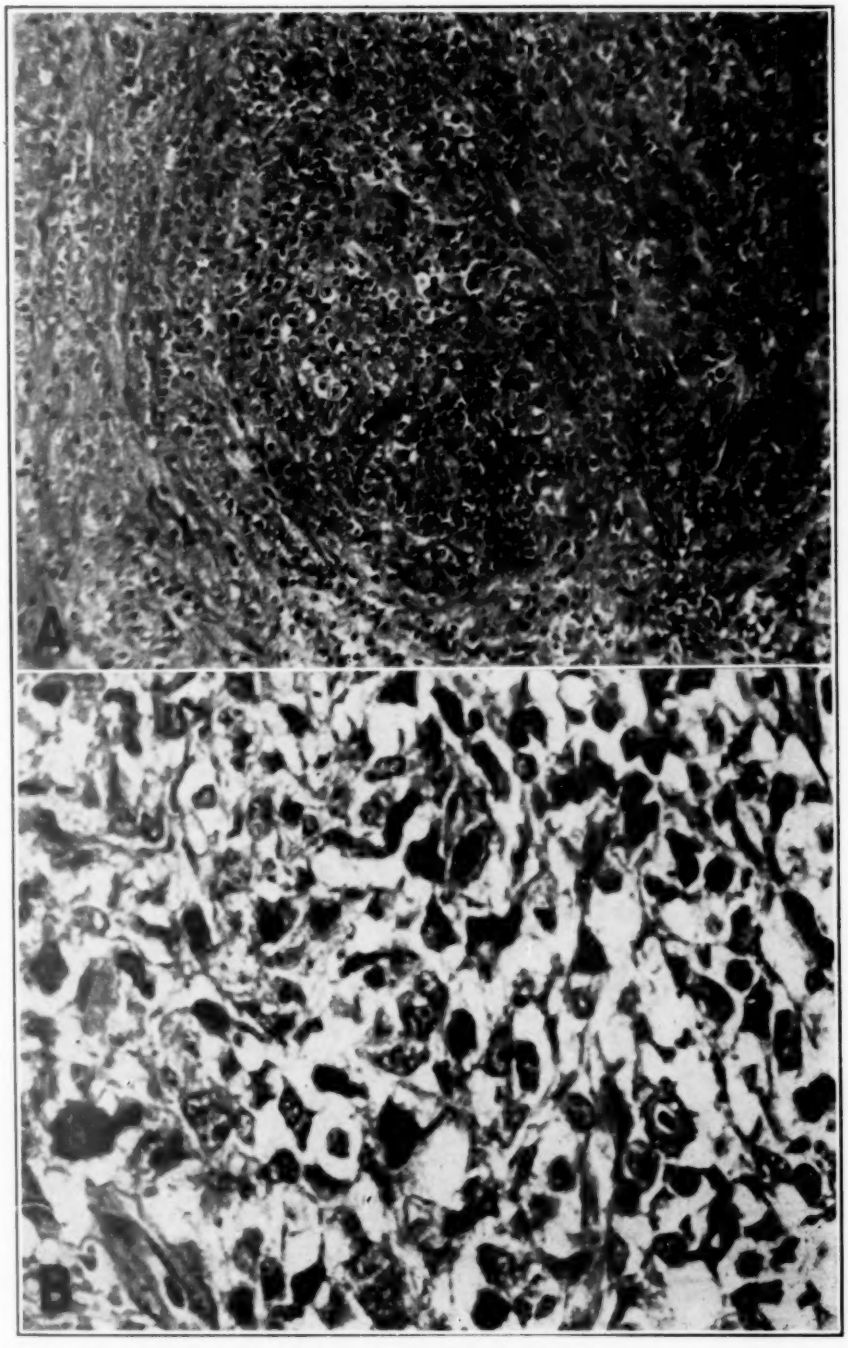

PLATE 6. White male, 22. Duration 28 months. Radiotherapy 1350 r.

A. Biopsy (lymph node): Hodgkin's granuloma; fibrosis was conspicuous prior to irradiation (X190).

B. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma; the area shown is representative of all growths found at autopsy, the tumor being composed of moderately well differentiated stellate reticulum cells. No residual fibrosis was evident (X750).

(A.I.P. Acc. 37635. Neg. Nos. 94672, -693.)

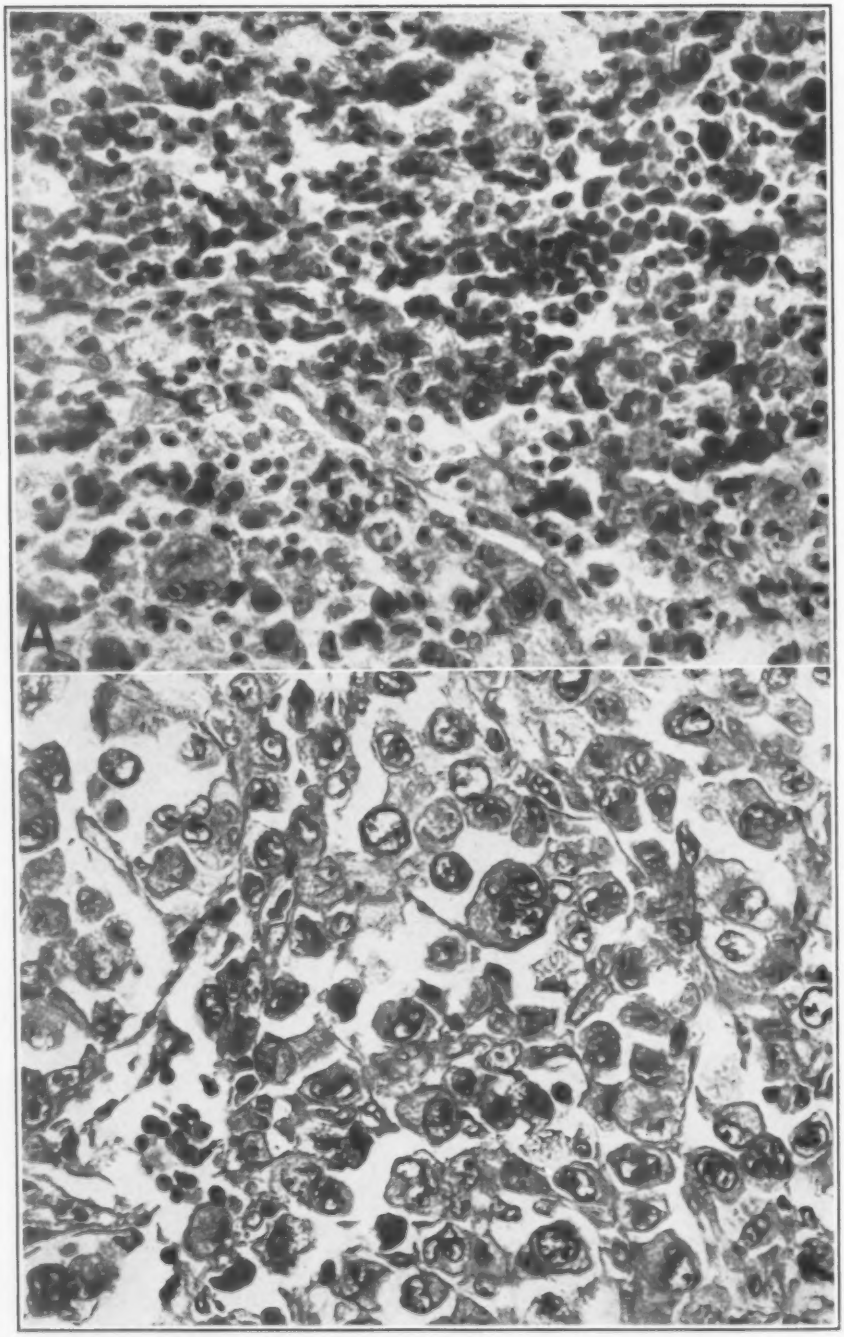

PLATE 7. White male, 22. Duration 4 months. Radiotherapy, none.

A. Biopsy (lymph node): Hodgkin's granuloma, characterized by a multiplicity of cell types, including many eosinophils (X600).

B. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma; an unusual variant with huge tumor cells, all the more striking by comparison with A, photographed at the same magnification (X600). (A.I.P. Acc. 104376. Neg. Nos. 92993, -994.)

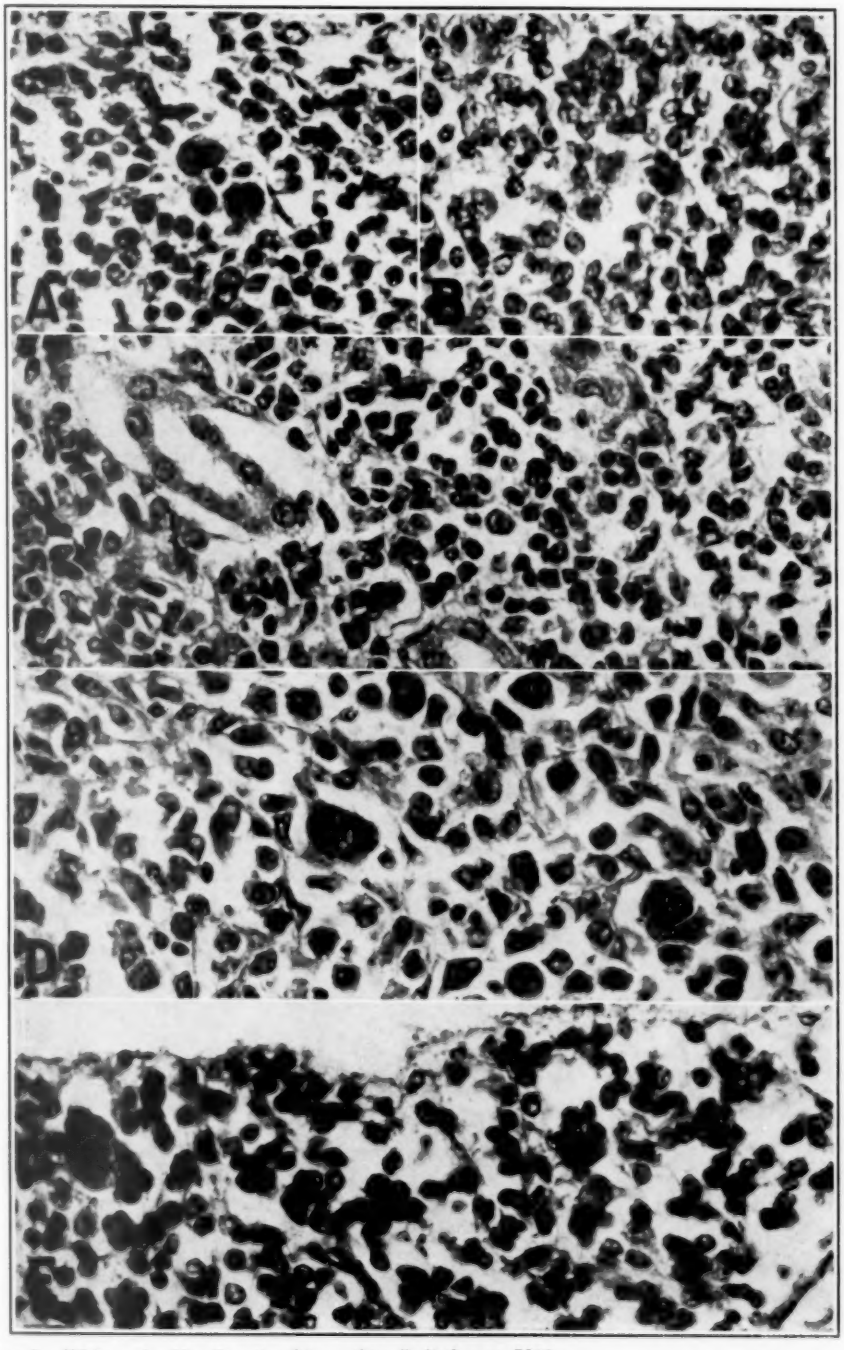

PLATE 8. White male, 28. Duration 24 months. Radiotherapy 5200 r.

A. 1st biopsy (lymph node): Hodgkin's paragranuloma; small lymphocytes take the foreground, with occasional reticulum cells and Reed-Sternberg cells (center) (X600).

B. 2nd biopsy (lymph node): Lymphoid cells are larger and have vesicular nuclei, but the general pattern is still a uniform one (X600).

C. Autopsy (kidney): A diffuse infiltration of small lymphocytes spreads tubules apart without destroying them, in a fashion usually found in lymphatic leukemia (X600).

D. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma; this multiform pattern was limited to the lymph nodes (X600).

E. Autopsy (meninges): This uniform small lymphocyte infiltration resembles that in the kidneys (X600). (A.I.P. Acc. 125695. Neg. Nos. 93029, -030, -031, -032, -034.)

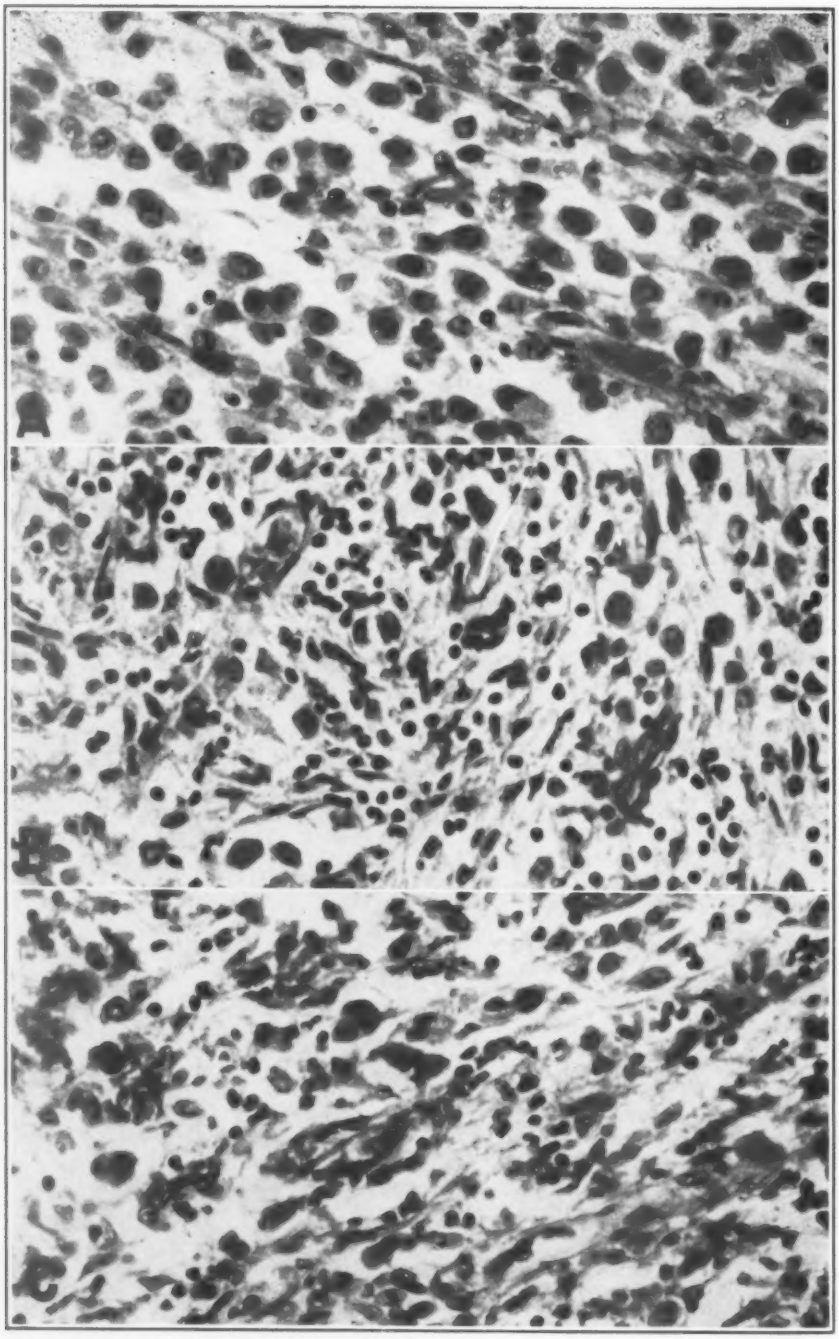

PLATE 9. White male, 23. Duration 3 months. Radiotherapy, none.
3 areas from the original lymph node biopsy.

A. 1st area: Tumor composed of fairly uniform lymphoid cells which are large and have vesicular nuclei with nucleoli (lymphosarcoma, lymphoblastic type) (X600).

B. 2nd area: Granulomatous pattern with sparse sprinkling of lymphoblastic tumor cells (X600).

C. 3rd area: Granulomatous pattern, but with predominance of angioblasts and new capillary formation (X600).

(A.I.P. Acc. 133580. Neg. Nos. 92988, -989, -990.)

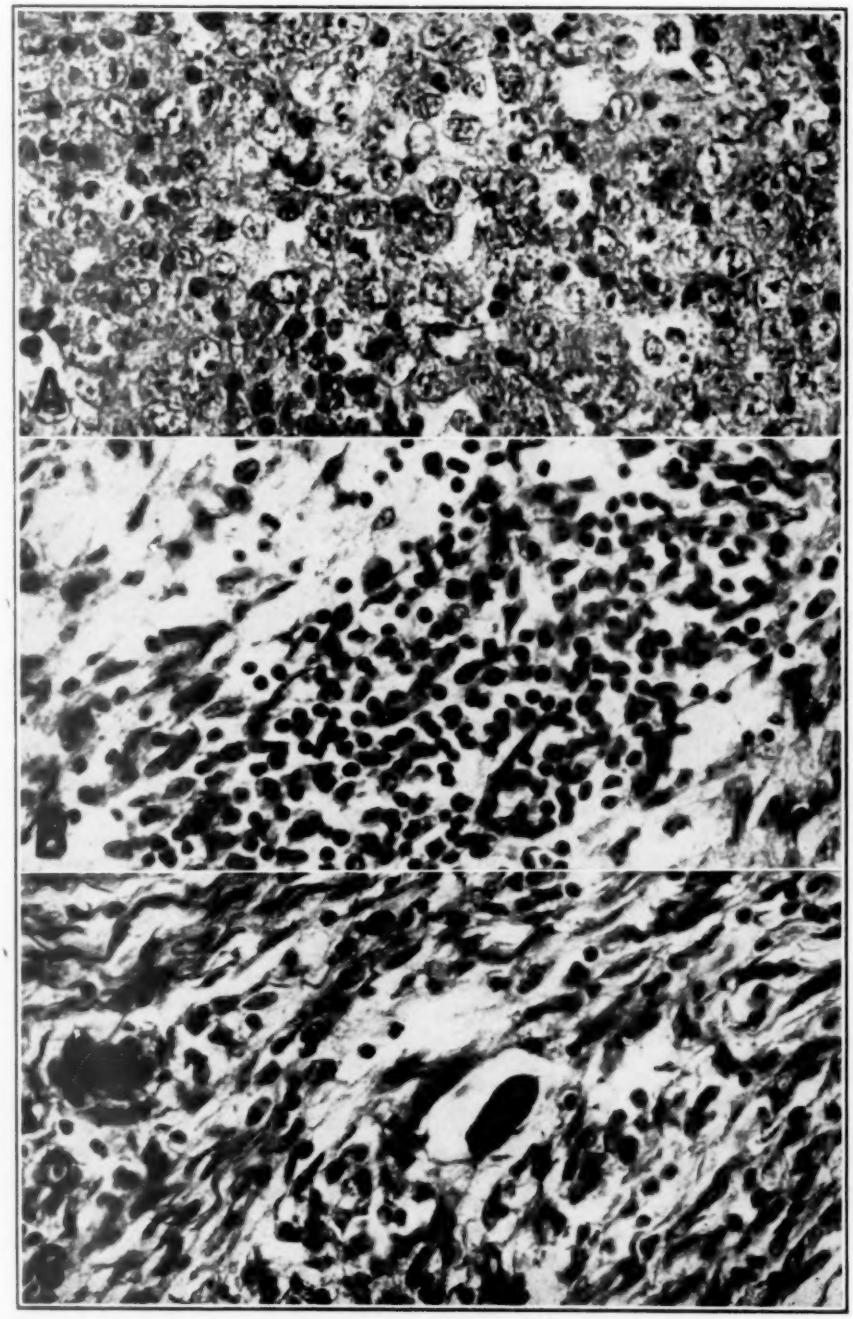

PLATE 10.—White male, 19. Duration 2 months. Radiotherapy, none.

A. 1st biopsy (lymph node): Reticulum cell sarcoma, undifferentiated (syncytial) type (X600).

B. 2nd biopsy (lymph node): Granuloma with admixture of lymphocytes, reticulum cells, and fibroblasts (X600).

C. Autopsy (lymph node): Hodgkin's granuloma; fibrosis is more pronounced, and smudged giant cells of Reed-Sternberg type are interspersed (X600).

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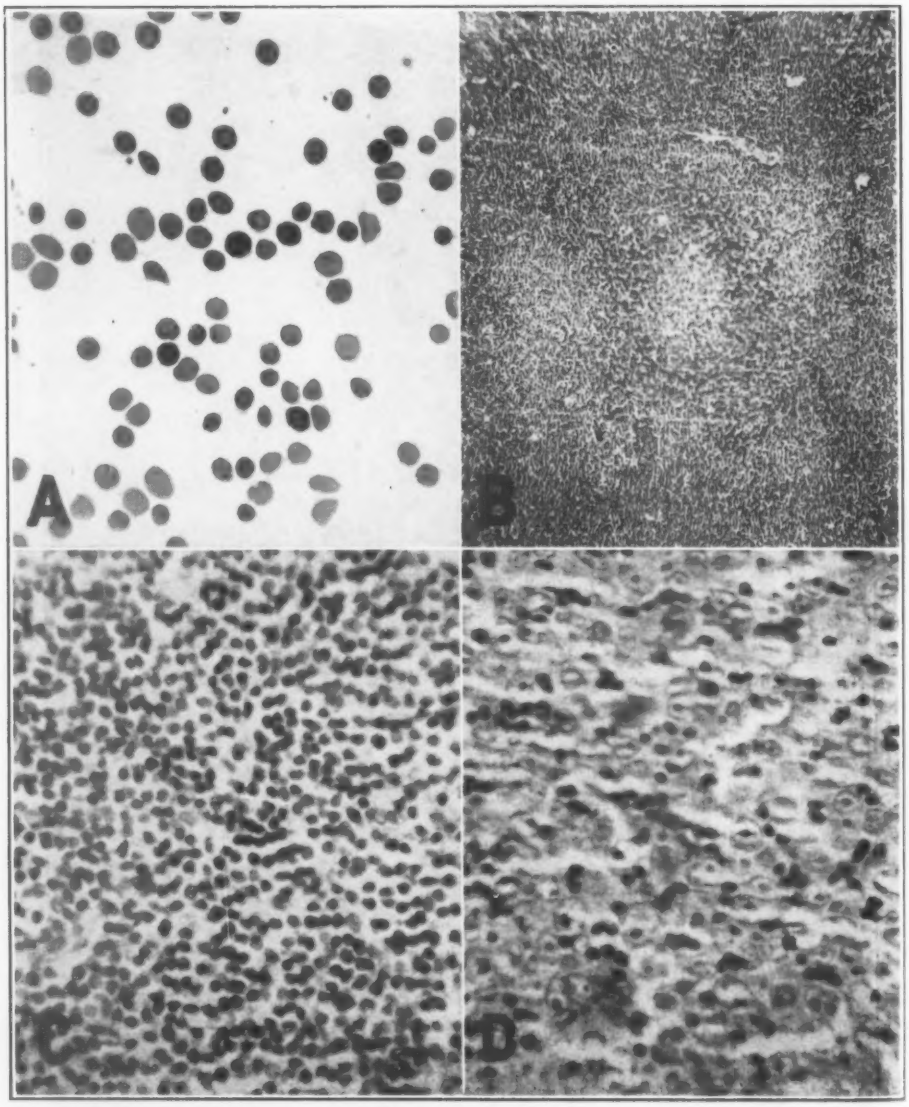

PLATE 11. White male, 20s. Duration unknown. Radiotherapy, none.

A. Blood Film: Typical blood picture of chronic lymphatic leukemia with virtually all circulating leukocytes being of well differentiated lymphocytic type (X675).

B. Biopsy (lymph node): Photomicrograph at low magnification discloses vestiges of follicular lymphoblastoma in one portion of the node (X60).

C. Biopsy (*same* lymph node): Other parts of the lymph node have completely lost the follicular pattern and show diffuse sheets of well differentiated lymphocytes, the appearances being consistent with either chronic lymphatic leukemia or a small cell type of lymphosarcoma (X600).

D. Biopsy (*same* lymph node): Still other large areas are made up of fairly uniform sheets of anaplastic reticulum cells, conforming to the so-called syncytial type of reticulum cell sarcoma (X600). Note that photomicrographs C and D were taken at the same magnification.

(Neg. Nos. PH, NS-1, 2, 3, 4.)

quently encountered change was from Hodgkin's granuloma to Hodgkin's (reticulum cell) sarcoma. Next in order was Hodgkin's paragranuloma to granuloma. Of the 6 paragranulomas that appeared to transform directly to sarcoma, one showed a combination of reticulum cell sarcoma and lymphosarcoma types, the two variants being distinct in separate foci. Two follicular lymphoblastomas underwent transition to Hodgkin's sarcoma, one to granuloma, and one to paragranuloma. Early biopsies on 13 patients disclosed a more poorly differentiated tumor than we found either in later biopsies or at autopsy; it is not clear whether this represented a transition toward better differentiation, or whether the biopsy fortuitously disclosed a local variant of the major type of pattern.

The variety of histologic appearances observed in different foci in the same individual, and even in several areas in the same lymph node, was still more spectacular (Table 3). Thus, 384 of 700 cases presented these combined lesions. In addition to the conventional types of lymphoma, 8 cases showed areas of tumor which, if viewed alone, would justify the diagnosis of fibrosarcoma. This is not particularly odd, however, as fibroblasts are derived from the primitive mesenchyme and participate largely in the granulomatous form of Hodgkin's disease; fibrosarcomatous lesions occurred in patients who had had no radiotherapy, as well as in individuals who were treated.

Lymphomas not grouped with Hodgkin's disease also exhibited alteration of their histologic structure in much the same fashion, as indicated in the periphery of the diagram (Fig. 1). This series included many cases of reticulum cell sarcoma which did not obviously develop from Hodgkin's paragranuloma or granuloma, being found either in pure form or having resulted from a direct transition of follicular lymphoblastoma or lymphosarcoma; such changes are not readily apparent from the scheme of interrelationship presented in Fig. 1, which was devised for the sake of simplification. Tumors at first classified as reticulum cell sarcoma also ended as lymphosarcoma. Likewise, chronic lymphatic leukemia sometimes preceded the development of large tumefactions indistinguishable from lymphosarcoma, and patients with typical lymphosarcoma occasionally produced the blood picture of lymphatic leukemia. An analogous situation occurred with respect to reticulum cell sarcoma and monocytic leukemia. Finally, a few cases of follicular lymphoblastoma terminated as lymphatic leukemia. Our series did not include an instance of monocytic leukemia in which a precursor stage of follicular lymphoblastoma was identified, but this is regarded as a distinct probability.

Summary. This study confirms and extends the opinions of other authors that a rigid subclassification of lymphatic tumors is artificial and confusing. Analysis of 1300 lymphatic tumors, many sampled several times during their progress, showed a striking fluidity in histologic pattern, with transitions and combinations that could best be interpreted as indicating a single neoplastic entity having a number of variants.

All photomicrographs reduced 10% below the magnifications noted in the legends.

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A HEMATOLOGICAL AND HISTOLOGICAL STUDY OF THE BONE MARROW AND PERIPHERAL BLOOD OF THE ADULT DOG*

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THE medical literature contains relatively few qualitative and quantitative data on the cellular content of the bone marrow of the dog. More recent publications include the work of Alexandrov,[1] Van Loon and Clark,[11] Stasney and Higgins[10] and Mulligan.[7] Some of these investigators obtained marrow from living dogs by sternal puncture or rib resection. Others obtained marrow for examination from specimens of rib and femur taken at autopsy. The methods employed for these studies included differential counts of the marrow as measured from a smear preparation and sometimes supplemented with an imprint or histopathological examination. The so-called total nucleated cell count was rarely, if ever, employed to indicate the cellularity of the bone marrow.

There have been numerous reports on the normal blood cytology of the dog.[2,4,5,6,8,9]

The purpose of this report is to indicate the findings in the bone marrow of a carefully selected group of normal adult dogs as measured by combined hematological and histological examination.

The hematological picture in the peripheral blood of normal adult dogs is included.

Methods. Adult mongrel dogs of both sexes between 9 to 24 months of age, weighing between 8 and 20 lbs., were used. All dogs were judged normal and in good health by standard laboratory examinations, received a standard kennel ration of Friskies or Purina dog chow, and had been subjected to deworming and distemper vaccination procedures at least one month previously.

The animals were trained to be postured on a table for bleeding purposes. Venepunctures without stasis were made from the jugular vein at a standard time each morning when the animal was in a fasting state. A standard amount of blood was delivered to a small bottle containing a mixture of dried ammonium and potassium oxalate. Samples of blood for the differential white blood cell count and platelet determinations were taken directly from the needle while in the vein.

Red blood cell and total white blood cell counts were made by standard techniques employing haemacytometer diluting Thoma pipettes and Spencer bright line Neubauer counting chambers. All determinations were made in duplicate, and if the results did not check within 10%, recounts were made from the blood in the KNH_4 oxalate bottle.

Differential white blood cell counts

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were made from cover slip smears stained with Wright's stain. A minimum of 100 cells was counted.

For the platelet counts, the blood was diluted in a red blood cell pipette with platelet solution containing brilliant cresyl blue, sodium citrate and formalin and delivered on to the counting chamber.

Reticulocyte counts were made from cover slip smears containing 1% alcoholic solution of brilliant cresyl blue. One thousand red blood cells were counted and the number of reticulocytes expressed in per cent.

Hemoglobin was determined by diluting a standard volume of the blood sample in a pipette with 0.1 N HCl and comparing the color intensity with that of a standard dichromate solution in a colorimeter (Klett Summerson type) using a green (No. 54) filter. The final value was determined from a standard graph.

Sedimentation rate and hematocrit determinations were made after the method of Wintrobe.[12]

The bone marrow was studied from specimens of rib obtained by rib resection and from ribs, femora, humeri and tibiae obtained at autopsy. The time of sacrifice of the dog was carefully noted and preparations for study were usually executed immediately. In other instances, a marrow specimen remained in the sacrificed dog for a known period of time and was then prepared for examination. In this way it was believed more precise information could be obtained concerning post-mortem changes on the cellular composition of the bone marrow.

The dogs were prepared for rib resection with morphine sulfate supplemented by local infiltration of novocaine. An incision approximately 4 to 6 cm. was made over the rib to be resected and dissection carried down to the periosteum. The periosteum was split lengthwise and dissected from the rib by means of a periosteal elevator. A section of rib near but not involving the costo-chondral junction, approximately 4 to 6 cm. in length, was then resected with the aid of a small circular power saw. The periosteum and wound were closed with multiple interrupted sutures in layers. A section of the rib so removed was placed in Zenker's fixing fluid for histopathological examination. Hematological examination of the bone marrow was carried out as follows:

Total Nucleated Cell Count. A portion of the marrow was squeezed out of the rib, placed in a depression of a drop plate and agitated with a small glass stirring rod to homogenize the specimen. A portion of this marrow was drawn up to the 0.2 mark of a red blood cell pipette and diluted to the 1.01 mark with 2% acetic acid or Turk's solution, giving a dilution of 1 to 500. The pipette and its contents were placed in a shaker and agitated for 15 minutes. The first 3 drops of material were then discarded and the counting chamber filled as for a routine blood count. After allowing the cells to settle in the chamber for 3 minutes, a count was made from the 4 corner squares, each corner comprising 1 cu. mm.

$$\frac{\text{No. Cells counted}}{4} \times 500 \text{ (dilution)} \times 10$$

= No. of nucleated cells/mm^3 of marrow. If the count was expected to be either low or high, the dilution factor was varied accordingly.

Differential Cell Count. Cover slip smears were made from marrow to which an equal portion of homologous serum had been added. Smears were allowed to dry in the air and were then stained with Wright's stain. A minimum of 500 cells was counted, and the results were expressed in percentages.

An absolute marrow cell count was obtained by multiplying these percentages by the total nucleated cell count.

Results. A classification and description of the cells of the bone marrow employed in this study are submitted below. No single cell has been described herein as a common stem cell for both the erythroid and myeloid series. The myeloblast was regarded as the stem cell for the myeloid series and the megaloblast for the erythroid series. No cell was classified into one of these series unless its morphology justified its classification with certainty. Debatable cells were placed in the un-

classified group. Megakaryocytes have been included in this classification. It should be pointed out that the smear technique is not to be considered a satisfactory method for the demonstration of the presence or absence of megakaryocytes.

MYELOID SERIES. *Myeloblast:* This was a large cell, 25-30μ in diameter, frequently round, with a dark blue, non-granular, usually homogenous and occasionally vacuolated cytoplasm. The nucleus was sharply demarcated from the cytoplasm, filling ⅔–¾ of the cell. It was round, irregular, heavy blue-purple with dark staining properties containing readily discernible nucleoli and fine chromatin material.

Promyelocyte: This cell was usually the same size as the myeloblast. The nucleus was slightly smaller, had a more coarse chromatin meshwork and the nucleoli were decreased or absent; the cytoplasm was lighter and sometimes showed early azurophilic granulation.

Myelocyte: This cell occasionally showed a decrease in overall size. The cytoplasm was lighter in color with larger granules which were neutrophilic, eosinophilic or basophilic. The nucleus still comprised a large part of the cell, was round or irregular and less sharply demarcated because of the overlying cytoplasmic granulation. The chromatin material was more coarse and nucleoli were absent.

Juvenile Granulocyte: This cell was smaller and measured 15-25μ in diameter. The most distinctive feature was the indentation of the nucleus which was relatively smaller than the nuclei of the cells previously described. The chromatin structure was finer and the cytoplasm had a paler background in which the granulation was finer and less distinct.

Stab Neutrophil: The stab, staff or band cell was recognized by a smaller S or V or pleomorphic shaped nucleus and chromatin material which was coarse and stained darker than the nuclei of the juvenile granulocytes.

Segmented Neutrophil: The last stage in the maturation of the myeloid cell was illustrated by the segmented neutrophil. This cell measured 15–20μ in diameter, had a conspicuous segmented nucleus connected by filaments, and the cytoplasm, which was pale and fine, contained indistinct granulations.

The eosinophilic myelocyte series was similar to the neutrophil series except that the cytoplasmic granulation had distinct acidophilic properties. The granules were larger and more refractile. The basophilic series were, likewise, similar to the neutrophil series except that the granulation had basophilic properties.

ERYTHROID SERIES. *Megaloblast:* This cell was round, 15–20μ in diameter, had a dark blue, homogenous, scanty cytoplasm and a large medium purple, finely granular nucleus in which nucleoli were frequently found. A light or clear zone in the cytoplasm was usually noted.

Erythroblast: This cell was smaller than the myeloblast and measured 10–15μ in diameter. The cytoplasm was lighter in color and might or might not have had a clear zone. The nucleus was absolutely and relatively smaller with a more coarse dark purple chromatin structure.

Normoblast: A further decrease in size was shown, and the cytoplasm presented evidence of containing hemoglobin. The nucleus was less than ⅔ the size of the cell and, in some instances, was pyknotic or in the process of extrusion.

Megakaryocyte: This cell was readily identified by its large size (30–60μ) and multilobulated nucleus or multinuclei. The cytoplasm was pale

blue and occasionally very finely granular.

Lymphocyte: This cell did not differ appreciably from that found in the peripheral blood. Large lymphocytes were rarely found. The cell measured 7–15μ in diameter, had a pale, clear blue cytoplasm occasionally containing fine azurophilic granules. The nucleus was relatively large, rounded, usually eccentric and contained dense coarse chromatin. Subdivisions of this group were not deemed advisable.

Plasma Cell: This cell measured

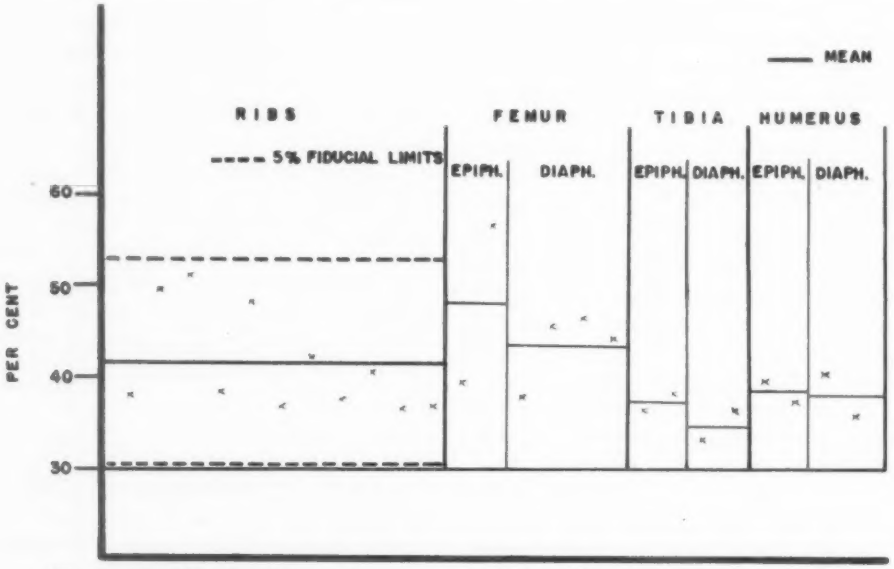

Fig. 1.—Total Erythroid Series from marrow of flat and long bones of a normal dog.

TABLE 1. ANALYSIS OF THE PERIPHERAL BLOOD FOR 91 NORMAL DOGS

Blood Element	*Range*	*Mean*	σ
Red Blood Count (1,000,000/mm³)	4.5–8.8	6.22	.697
Hemoglobin (Grams %)	11.2–19.5	14.78	1.730
Reticulocytes (%)	0–2.7	.78	.565
Platelets (100,000/mm³)	0–4.2	2.27	.649
White Blood Count (1,000/mm³)	545–27,950	10,582	3,544
Absolute Neutrophils (1,000/mm³)	3,190–25,994	8,074	3,600
Absolute Lymphocytes (1,000/mm³)	0–5,788	1,689	1,019
Differential White Count			
Neutrophils %	42–99	75.11	12.18
Eosinophils %	0–39	6.88	6.48
Basophils %	0–3	.14	.44
Lymphocytes %	0–55	16.82	9.88
Monocytes %	0–4	.15	.54
Myelocytes %	0	0	—
Blast Forms %	0–6	.90	1.14
Plasma Cells %	0	0	—
Basophilic Stippling	0	0	—

CORRECTED SEDIMENTATION RATES FOR 75 NORMAL ADULT DOGS

Sedimentation Rate (mm per hour)			*Hematocrit (per cent)*		
Range	*Mean*	σ	*Range*	*Mean*	σ
0–25	3.3	5.4	40–70	51.3	5.5

TABLE 2. BONE MARROW DIFFERENTIAL COUNT FOR RIBS, FEMORA, TIBIAE AND HUMERI
Mean Values for Normal Dogs

		RIBS		FEMORA				TIBIAE				HUMERI			
				Epiphysis		Diaphysis		Epiphysis		Diaphysis		Epiphysis		Diaphysis	
SERIES	CELL TYPE	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ
Myeloid	Myeloblasts	1.77	.92	2.20	.76	2.53	1.26	2.35	.72	1.82	1.46	2.38	1.03	2.77	1.13
	Promyelocytes	.44	.56	.23	.50	.21	.39	.96	1.06	.27	.40	.48	.80	.42	.72
	Myelocytes	1.42	.94	1.19	1.24	1.30	1.16	1.97	.76	1.46	1.21	1.74	1.77	.89	1.12
	Juveniles	3.64	2.80	2.36	1.78	3.34	2.86	3.56	2.27	3.72	2.73	4.32	2.74	4.16	2.46
	Stabs	33.42	7.80	35.01	6.33	34.12	6.14	34.62	5.27	41.40	11.47	33.05	3.84	35.51	4.32
	Neutrophils	2.57	1.72	4.94	2.50	3.70	2.15	6.31	1.98	7.15	3.31	4.81	2.50	5.26	1.45
	Eosinophils	9.83	5.32	8.39	4.22	9.84	5.14	10.54	5.95	8.63	5.93	9.98	5.05	9.40	5.51
	Basophils	.41	.84	.20	.22	.41	.58	.46	.46	.16	.32	.53	.67	.35	.37
Total Myeloid*		53.51	9.71	54.53	7.21	55.45	8.04	60.78	3.80	64.61	11.09	57.30	4.05	58.76	4.39
Lymphoid	Lymphocytes	2.16	2.59	1.32	1.49	2.59	2.94	1.76	2.36	5.00	6.98	2.62	3.86	3.66	3.97
Monocytic	Monocytes	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Erythroid	Megaloblasts	.28	.34	.14	.30	.12	.19	.09	.16	.25	.56	.08	.15	.13	.18
	Normoblasts	6.87	3.76	7.76	4.08	7.21	4.32	5.57	3.08	4.80	4.04	5.80	3.12	5.12	3.15
	Erythroblasts	32.88	9.94	31.19	5.80	28.13	4.17	26.00	2.48	16.58	7.90	28.41	4.99	26.81	3.42
Total Erythroid*		40.03	12.02	39.09	9.01	35.46	6.44	31.65	4.54	21.63	11.62	34.28	6.72	32.06	5.22
Plasma Cell	Plasma Cell	.89	.60	.99	.91	1.57	.96	1.34	.90	1.17	1.10	1.45	1.17	1.29	.67
Megakaryocyte	Megakaryocyte	0	0	0	0	0	0	0	0	0	0	0	0	.03	.10
Unclassified	Unclassified I	.91	.58	.81	.85	.82	.66	.47	.45	.27	.40	.92	.51	.97	.54
	Unclassified II	2.28	2.68	3.12	3.47	3.83	4.46	3.78	3.88	7.10	7.33	3.34	3.34	3.11	3.16
	Unclassified III	.21	.30	.14	.27	.28	.33	.22	.33	.21	.39	.10	.18	.11	.21
Total Unclassified*		3.41	2.74	4.07	3.52	4.92	4.15	4.47	3.60	7.58	7.23	4.36	3.26	4.19	3.02
Myeloid/Erythroid Ratio		1.34		1.39		1.56		1.92		2.99		1.67		1.83	
No. of Sites		35		8		16		8		8		8		8	

* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.

10–15μ in diameter, had a round, perinuclear clear area and a fairly dark blue, homogenous cytoplasm with a light zone in it. The nucleus was relatively small, eccentric and rounded in which the chromatin material was coarse and sometimes had a cartwheel pattern.

Unclassified Cells: When cells were found to present a fairly consistent

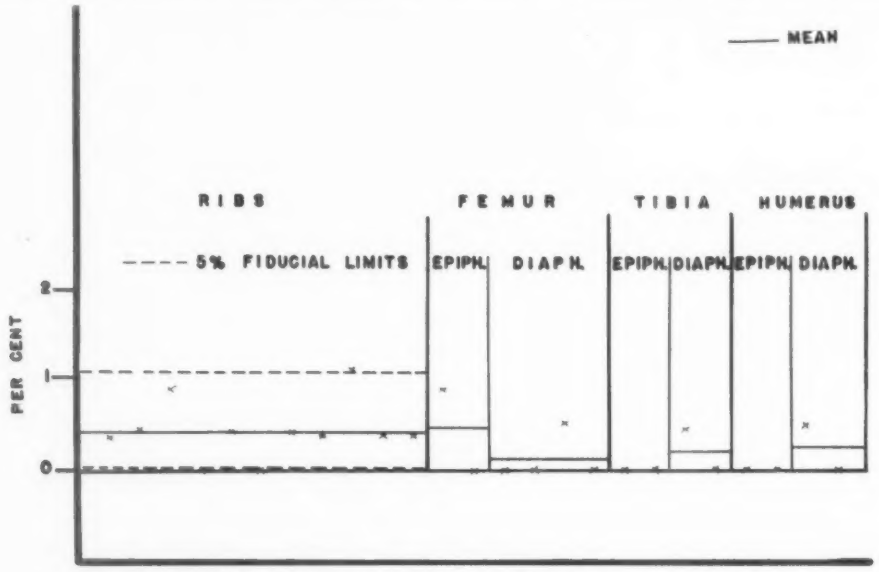

Fig. 2.–Megaloblasts from marrow of flat and long bones of a normal dog.

TABLE 3. RIB BONE MARROW DIFFERENTIAL ANALYSIS FOR NORMAL DOGS

Series	*Cell Type*	*Minimum*	*Maximum*	*Mean*	*Sigma*
Myeloid	Myeloblasts	.23	3.66	1.89	.90
	Promyelocytes	0	3.26	.65	.97
	Myelocytes	0	9.47	2.73	2.40
	Juveniles	0	24.44	5.12	4.12
	Stabs	16.46	62.88	42.37	9.14
	Neutrophils	.24	14.29	5.01	3.41
	Eosinophils	.23	19.30	4.72	3.98
	Basophils	0	1.25	.19	.30
Total Myeloid*		36.71	90.07	62.68	11.78
Lymphoid	Lymphocytes	0	8.05	.73	1.42
Monocytic	Monocytes	0	0	0	0
Erythroid	Megaloblasts	0	1.33	.27	.38
	Normoblasts	0	11.22	4.64	3.09
	Erythroblasts	7.98	53.92	28.24	10.24
Total Erythroid*		8.72	60.50	33.15	11.69
Plasma Cell	Plasma Cell	0	2.08	.39	.66
Megakaryocyte	Megakaryocyte	0	1.10	.06	.21
Unclassified	Unclassified I	0	2.47	.78	.60
	Unclassified II	0	15.51	1.97	2.88
	Unclassified III	0	1.46	.26	.34
Total Unclassified*		0	15.74	2.99	3.00
Myeloid/Erythroid Ratio				1.89	

Analysis Computed from 36 Dogs.

* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of mean with the total mean is only approximate.

picture but still could not be classified in the above groups, they were placed in subgroups as follows:

1. Cells of the erythroid and myeloid series that were undergoing mitotic and amitotic division.

2. Cells similar to small lymphocytes. These cells contained such a small amount of cytoplasm that identification was difficult.

3. These cells varied in size from 5–20μ in diameter, had a grayish blue cytoplasm which sometimes contained large blue granules and was occasionally vacuolated. The nucleus was rarely distinguishable; if present, it occupied ¼ of the cell.

An analysis of the peripheral blood for 91 normal, adult dogs is presented in Table 1. These data are in general agreement with those of Van Loon and Clark[11] and others.

Data from the marrow differential counts of the ribs, humeri, femora and tibiae for a group of 4 dogs are shown in Table 2 and Figures 1 to 7 while Table 3 presents rib marrow data from 36 dogs. A survey of these tables shows that there is a definite similarity in the percentage distribution of the bone marrow cells in the 4 areas studied and between the diaphysis and epiphysis of the long bones. The myeloid-erythroid ratio is similar in all areas.

The means of the total nucleated cell count for femora, tibiae and humeri for the same 4 dogs individually are given in Table 4. The cellularity of the bone marrow from various regions of the body is compared. These data indicate that rib marrow is uniformly cellular throughout, whereas the cellular density of the long bones undergoes wide variations.

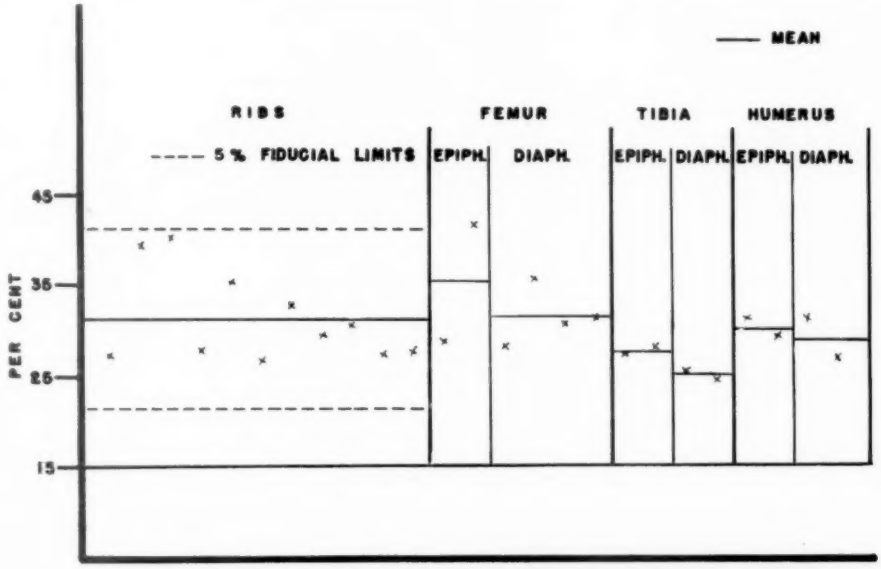

Fig. 3.—Erythroblasts from marrow of flat and long bones of a normal dog.

Table 5 compares the cellularity and differential counts in several rib sites of the same dog. These data indicate that bone marrow from various ribs presents a uniform picture with respect to cellular density and distribution.

The effect of time after death on rib marrow is shown in Table 6. No significant differences in the percent-

TABLE 4. BONE MARROW TOTAL NUCLEATED CELL COUNTS
Mean Values

DOG	RIBS	FEMUR		TIBIA		HUMERUS	
		*Epiphysis (2)**	*Diaphysis (4)*	*Epiphysis (2)*	*Diaphysis (2)*	*Epiphysis (2)*	*Diaphysis (2)*
1	(6)* 1,794,792	721,250	21,875	555,000	625	339,375	490,000
2	(10) 787,750	934,375	119,062	325,000	25,625	1,028,125	361,875
3	(11) 1,448,091	2,255,625	1,884,375	1,306,250	1,235,000	2,204,375	1,992,500
4	(8) 948,750	576,250	509,062	1,200,625	43,125	662,500	840,625

* Figure in parenthesis indicates number of specimens studied.

TABLE 5. BONE MARROW ANALYSIS OF VARIOUS RIB SITES FROM THE SAME DOG

SERIES	CELL TYPE	*8 RIB RT.*	*8 RIB LT.*	*9 RIB RT.*	*9 RIB LT.*	*10 RIB RT.*	*MEAN*	*σ*
Myeloid	Myeloblasts	2.59	.51	2.53	.74	2.13	1.70	1.000
	Promyelocytes	0	0	0	0	0	0	0
	Myelocytes	5.39	.76	8.05	5.69	6.38	5.25	2.715
	Juveniles	3.45	4.55	3.45	6.19	3.55	4.24	1.186
	Stabs	38.79	47.98	37.01	42.57	37.12	40.69	4.652
	Neutrophils	7.33	7.32	8.28	6.68	8.27	7.58	.690
	Eosinophils	3.67	3.28	4.37	3.96	5.20	4.10	.735
	Basophils	0	0	0	0	.24	.05	.107
Total Myeloid*		61.21	64.39	63.68	65.84	62.88	63.60	1.732
Lymphoid	Lymphocytes	.22	.25	0	0	.24	.14	.130
Monocytic	Monocytes	0	0	0	0	0	0	0
Erythroid	Megaloblasts	.22	0	.69	0	.24	.23	.282
	Erythroblasts	25.43	28.28	27.82	27.97	28.13	27.53	1.184
	Normoblasts	9.48	2.27	4.37	2.48	2.13	4.15	3.117
Total Erythroid*		35.13	30.56	32.87	30.45	30.50	31.90	2.076
Plasma Cell	Plasma Cell	0	0	0	0	0	.09	.192
Megakaryocyte	Megakaryocyte	.43	0	.23	0	0	.05	.103
Unclassified	Unclassified I	.86	1.01	.92	.74	.71	.85	.125
	Unclassified II	2.16	3.79	2.30	2.97	5.67	3.38	1.435
	Unclassified III	0	0	0	0	0	0	0
Total Unclassified*		3.02	4.80	3.22	3.71	6.38	4.23	1.388
Myeloid/Erythroid Ratio		1.74	2.11	1.94	2.16	2.06	1.99	
Total Nucleated Cell Count		1,161,250	1,092,500	1,118,750	1,076,250	960,000	1,081,750	75,263.1

* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.

Total Nucleated Cell Count		1,161,250	1,092,500	1,118,750	1,076,250	960,000	1,081,750	75,265.4

* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.

TABLE 6. RIB BONE MARROW ANALYSIS FOR NORMAL DOGS

Mean Values

SERIES	CELL TYPE	HOURS AFTER DEATH 0	2	3	4	5	8
Myeloid	Myeloblasts	1.56	.93	.56	3.25	.30	0
	Promyelocytes	.44	.55	0	1.18	0	0
	Myelocytes	1.18	.61	0	1.18	.30	0
	Juveniles	3.25	1.47	.28	2.78	0	0
	Stabs	31.54	31.06	28.81	42.78	17.76	30.04
	Neutrophils	2.53	1.79	.96	.24	1	1.74
	Eosinophils	8.73	8.70	8.60	9.76	1.,0	5.20
	Basophils	.59	.10	0	0	.30	0
Total Myeloid*		49.82	45.20	39.22	61.16	22.26	36.98
Lymphoid	Lymphocytes	1.03	.29	5.44	0	0	6.08
Monocytic	Monocytes	0	0	0	0	0	0
Erythroid	Megaloblasts	.26	.17	0	0	.48	0
	Erythroblasts	37.49	36.42	36.96	25.18	46.65	36.46
	Normoblasts	8.02	13.64	16.98	11.36	18.31	18.23
Total Erythroid*		45.77	50.23	53.94	36.54	65.45	54.69
Plasma Cell	Plasma Cell	.92	1.00	1.40	.92	.30	2.26
Megakarocyte	Megakarocyte	0	0	0	0	0	0
Unclassified	Unclassified I	.94	.18	0	.23	0	0
	Unclassified II	1.33	3.10	0	.92	11.98	0
	Unclassified III	.20	0	0	.23	0	0
Total Unclassified*		2.47	3.28	0	1.38	11.98	0
No. of Sites for Differential Count		14	6	2	2	2	2
Total Nucleated Cell Count		1,371,771	1,460,625	1,722,500	957,500	1,775,000	1,398,750
No. of Sites for Nucleated Count		14	6	2	4	2	2
Myeloid/Erythroid Ratio		1.09	0.90	0.73	1.67	0.34	0.68

* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.

ages or total nucleated cell counts are shown for the period studied.

Histological records of the rib and diaphysis of the femur are shown in Figures 8, 9.

Discussion. These results indicate that the cellular distribution as found in a given sample of bone marrow from one area of the body will be representative of the marrow picture from the rest of the body. This finding is in agreement with the observation of Stasney and Higgins.[10]

Bone marrow may be divided into 2 types: the more and constant cellular as found in the flat bones, and the less and more varied cellular as found in the long bones. However, there may be centers of hematopoietic activity distributed throughout the fatty marrow in the long bones. This is especially so adjacent to the endosteum and near the epiphysis. Thus the degree of cellularity of the flat bones in a normal or pathological state may be appraised by a total nucleated cell count or a histological preparation, but these determinations carry less significance in evaluating the fatty types of marrow. The sampling of marrow from the flat bones, such as the rib or sternum, will give not only an index of the cellular pattern but an index of the degree of cellularity as well. When sampling marrow bearing areas by needle and aspiration technique, local hemorrhage is invariably produced resulting in dilution of the marrow material by the shed blood. Subsequent samplings from the same site are altered by the reparative process from the previous hemorrhage. This reparative process is a slow one extending over many weeks, and residual damage can usually be detected months later, especially in the long bones.

Histological examination of the bone marrow entails many limitations, chief of which is lack of detailed individual cellular morphology and the associated inaccurate cellular identification. However, the megakaryocytes as well as the anatomical relationship of the marrow cells to other tissues in the marrow bearing region can be studied better.

A significant alteration in cellularity

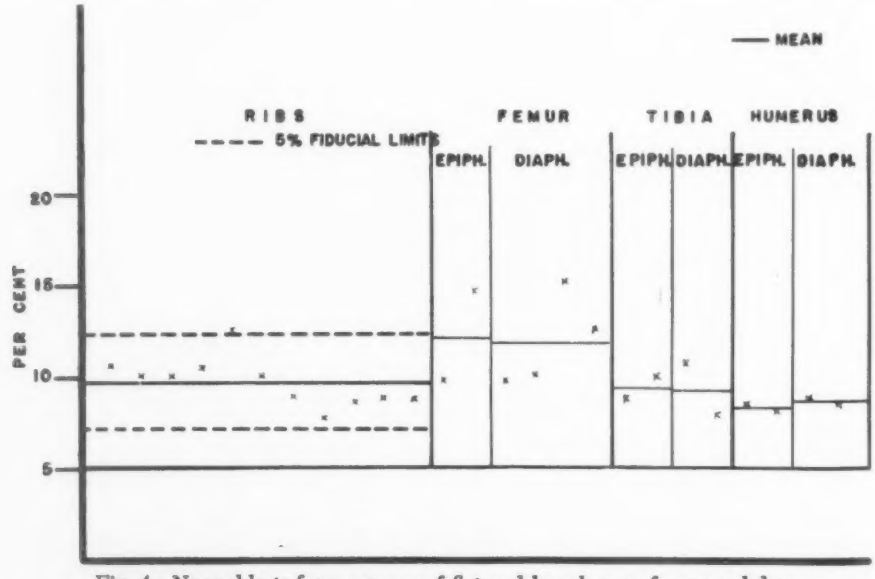

Fig. 4.—Normoblasts from marrow of flat and long bones of a normal dog.

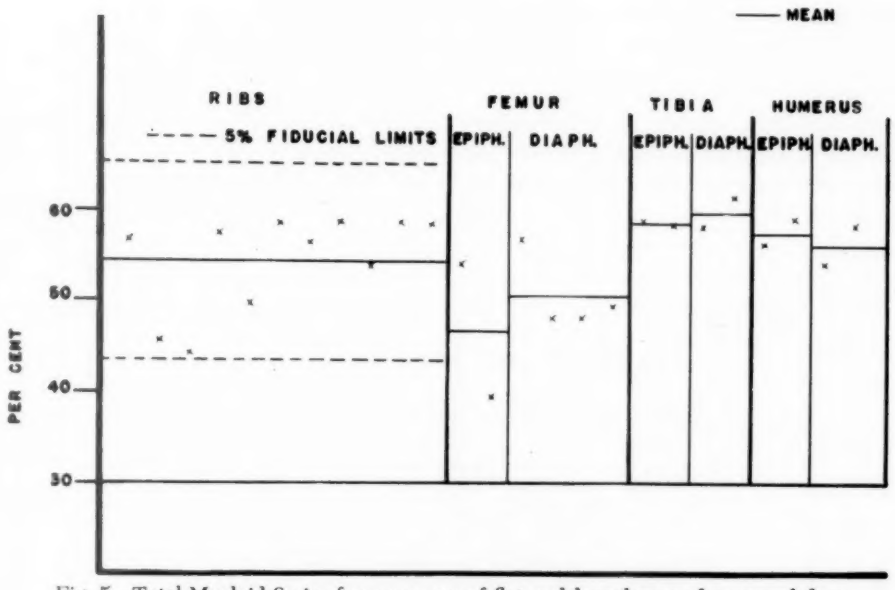

Fig. 5.—Total Myeloid Series from marrow of flat and long bones of a normal dog.

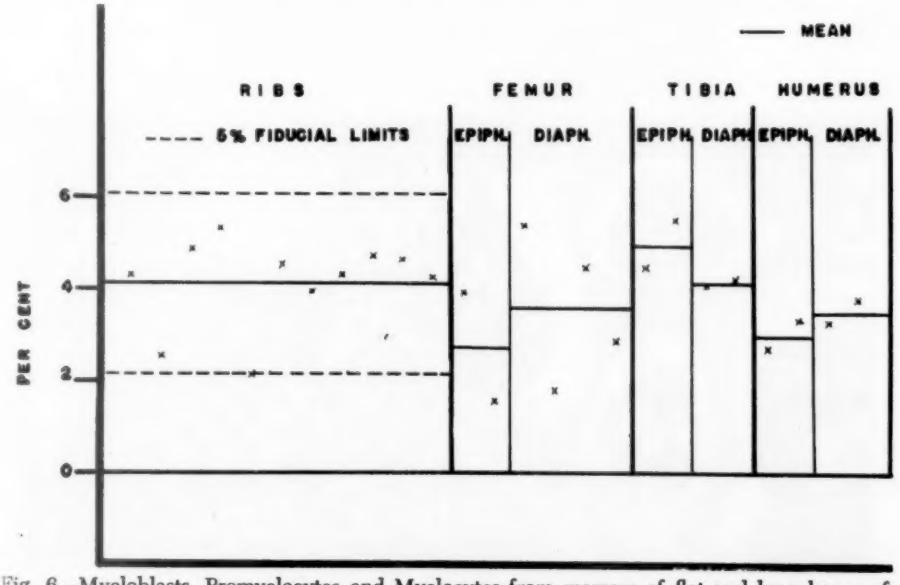

Fig. 6.—Myeloblasts, Promyelocytes and Myelocytes from marrow of flat and long bones of a normal dog.

and cellular detail of the marrow was not noted within the first 8 hours after death. Inasmuch as normal cellular morphology is intimately associated with cellular viability, it becomes important to determine whether or not cells, the marrow cells in particular, removed after death are viable. Green[3] has shown that many different types of cells can be readily transplanted in vivo when removed from the donor 8 hours or more after death. This lends evidence to the finding of an insignificant change of morphology within the first 8 hours after death.

The tabulation of somewhat high and

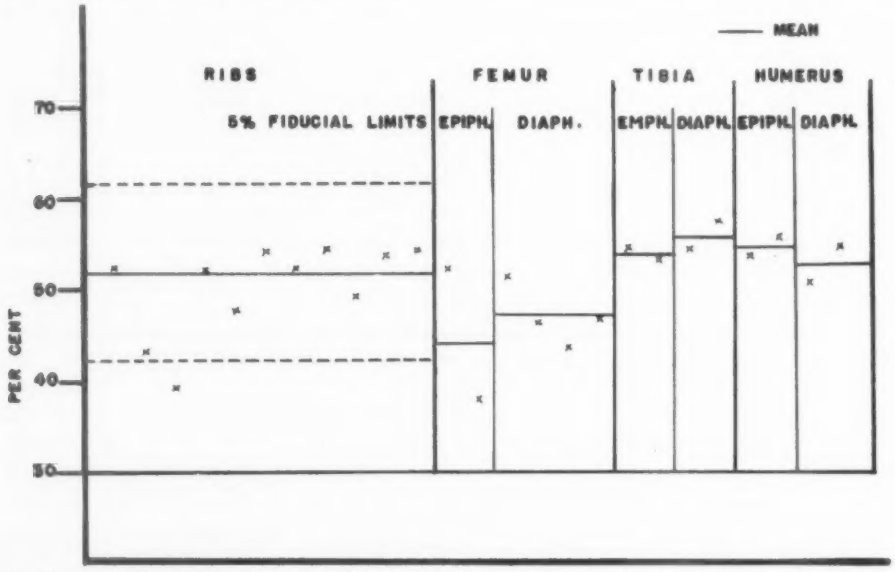

Fig. 7.—Juveniles, Stabs, Neutrophils, Eosinophils and Basophils from flat and long bones of a normal dog.

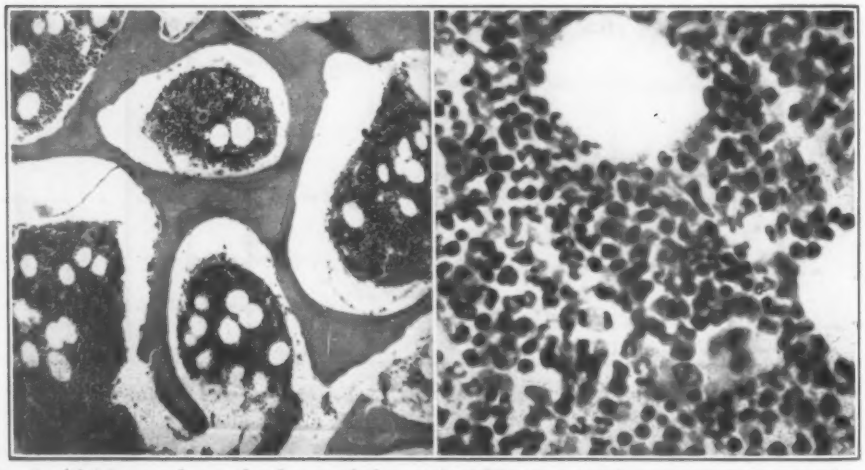

Fig. 8.—(a) Marrow from rib of normal dog ×100. (b) Same. Higher power ×650. Nucleated cells count 1,081,000 cells/mm³.

low values in the ranges of the peripheral blood was the result of, in most instances, isolated findings. The animals selected for this study were judged normal by conventional clinical standards but by hematological standards might not be accepted as normal.

Summary. 1. The bone marrow of ribs, femora, tibiae and humeri and the peripheral blood of adult normal dogs have been studied and the findings tabulated.

2. Methods for examination of the bone marrow of the dog are described.

3. Cellular distribution was shown to be fairly uniform throughout the marrow bearing areas of the dog, whereas the cellularity exhibited wide variations.

4. A significant alteration in degree of cellularity and cellular detail was not found in the bone marrow within the first 8 hours after death.

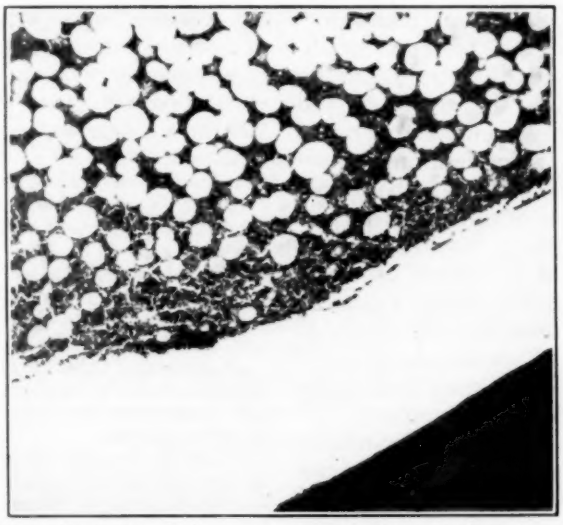

Fig. 9.—Marrow from diaphysis of femur of normal dog. Nucleated cells count 119,000 cells/mm^3 ×100.

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THE NEGATIVE EFFECT OF FOLIC ACID ON IRRADIATION LEUKOPENIA IN THE CAT*

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THE hemopoietic tissues are extremely sensitive to a variety of toxic agents such as: thiouracil, the sulfonamides, certain heavy metals, dinitrophenol, amidopyrine and roentgen irradiation. This sensitivity is reflected by alterations within these tissues and many times in the corpuscular elements of the peripheral blood resulting in anemia, leukopenia and thrombocytopenia. The attempts of physicians to prevent or correct these disorders by the administration of a variety of drugs have met with dismal failure. Certainly it must be admitted that the results of administration of pentnucleotide (to mention one drug) in granulocytopenia have been far from spectacular.

Following the isolation and synthesis of folic acid in 1945 and 1946 by Angier *et al.*,[1] this substance has been used widely in a variety of hemopoietic disorders. Watson *et al.*[4] have suggested that this drug may be useful in the correction of irradiation leukopenia. They obtained beneficial effects in humans receiving regional roentgen treatment for various types of malignancy. Therefore it was thought important to investigate the possible prophylactic and therapeutic value of folic acid in cats receiving whole body irradiation. It is realized that the situation which exists in human beings receiving regional irradiation is not strictly comparable to the whole body irradiation to which our cats have been subjected. Also the figures as given by Watson *et al.*[4] pertain to humans receiving repeated small doses of radiation in cases of malignancy, whereas this report deals with apparently normal cats receiving 200r at a single exposure.

Method: Twenty-six cats have been studied. They have been divided into 3 groups: Group I (6 cats) received both oral (50 mg.) and subcutaneous (30 mg.) folic acid** daily for one week prior to the exposure to 200r whole body irradiation.§ The folic acid was continued for 3 weeks following exposure to roentgen radiation. Daily white blood cell counts and differential studies were done for one week prior to irradiation and for one month subsequent to irradiation. All white blood cell counts were done with Bureau of Standards equipment.

Group II (9 cats). These animals received 50 mg. of folic acid subcutaneously daily for one week prior to Roentgen ray exposure. Folic acid was continued one month following such exposure. Subsequent study was the same as for Group I.

Group III (11 cats). These animals were kept as controls—that is they were exposed to the effects of 200r whole body irradiation and were not given folic acid. Follow-up study was the same as for animals in Group I.

Results.‡ These are shown clearly in Figs. 1, 2, 3, 4, and 5 which are a comparison of the normal and the control means of the various white blood cell elements. No difference between the control and the experimental animals can be detected.

* This paper is based on work performed under Contract Number W-7401-eng-49 for the Atomic Energy Project at the University of Rochester.

† Formerly Associate Professor of Medicine, University of Rochester School of Medicine.

** Courtesy of Dr. S. M. Hardy, Lederle Laboratories, Pearl River, New York.

§ Voltage 250 K.V.P.; Milliamperage 15; Target skin distance, 22 inches to center of cat; Filter, aluminum parabolic plus ½ mm. copper.

‡ These data have been subjected to statistical analysis and no significant statistical differences were detected in the results of the 3 groups of animals. This statistical work was done by the Statistical Department of The Atomic Energy Commission Project of the University of Rochester.

It can also be seen in Tables 1, 2 and 3 that there is no difference in the response to roentgen irradiation of cats given folic acid and those that were given no folic acid.

There also was apparently no difference between the cats in Group I and Group II. In other words, the route of administration of folic acid apparently did not influence the results.

Discussion. According to the theory of Stokes[3] folic acid acts as an enzyme or co-enzyme in the formation of thymine which is in turn converted

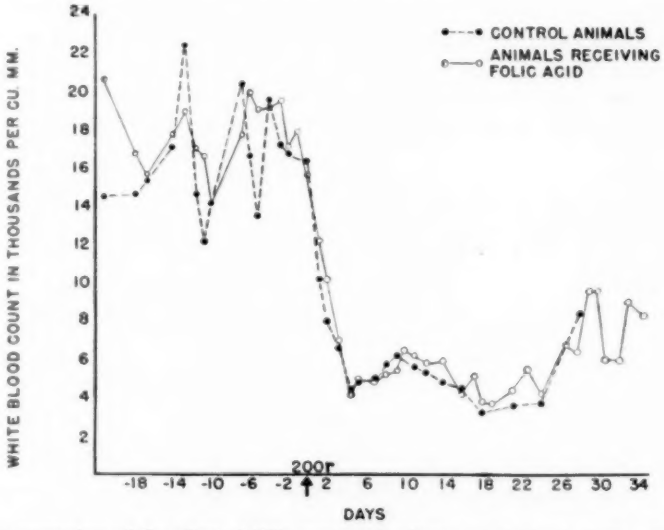

FIG. 1. A comparison of the effect of 200r roentgen irradiation on the level of the *white blood count* in cats receiving folic acid and in cats held as controls (receiving no folic acid).

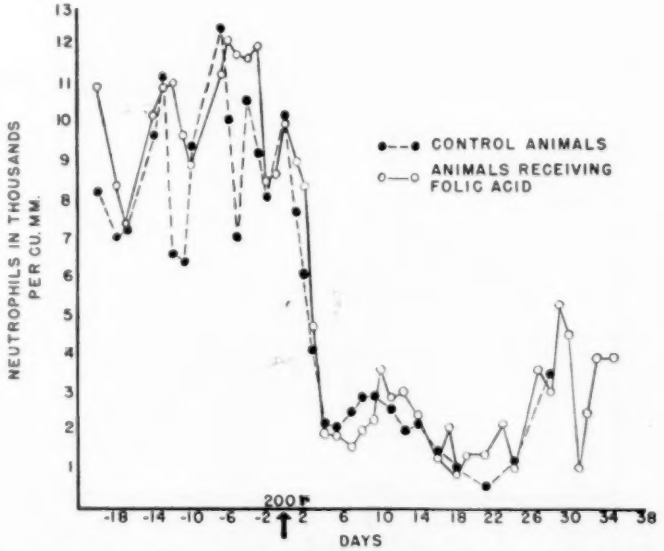

FIG. 2. A comparison of the effects of 200r roentgen irradiation on the level of the *neutrophils* in cats receiving folic acid and in cats held as controls (receiving no folic acid).

to nucleic acid, an integral part of the structure of the cell nucleus. There are many other theories as to the mode of action of folic acid but the discovery of its exact rôle in hemopoiesis must await further investigation. However, it may be said that folic acid probably plays an important rôle in normal hemopoiesis and that the lack of this substance may result in granulocytopenia and, or, anemia. Recently the effects of folic acid in the correction of various types of leukopenias have been studied by Kornberg *et al.*[2] The purpose of our investigation was to discover if possible if there were any beneficial effects obtained by the prophylactic or therapeutic administration of folic acid to cats receiving whole body roentgen irradiation. (It had been hoped, if such a beneficial effect could be obtained with folic acid, that it would be apparent by using an amount of roentgen radiation which was below the LD 50 for cats but yet sufficient to produce leukopenia in all instances.) This calcu-

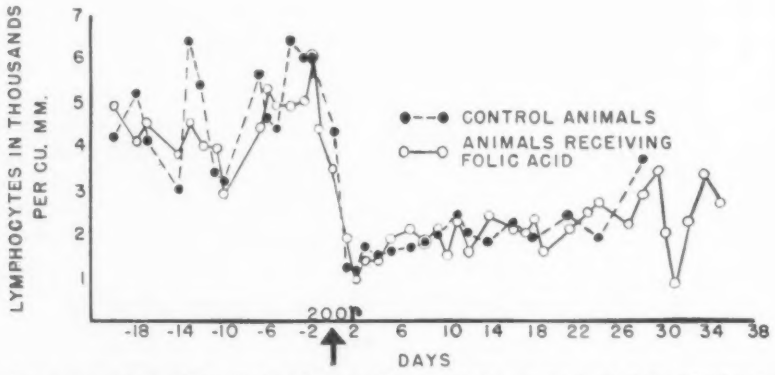

FIG. 3. A comparison of the effect of 200r roentgen irradiation on the level of the *lymphocytes* in cats receiving folic acid and in cats held as controls (receiving no folic acid).

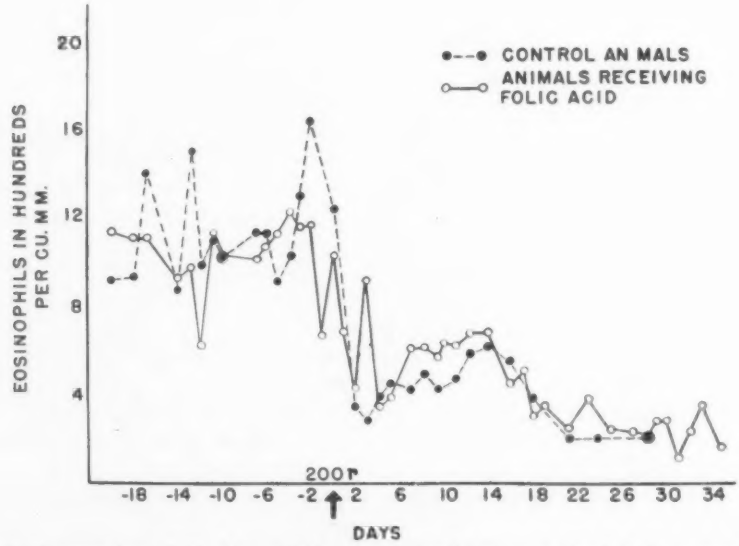

FIG. 4. A comparison of the effect of 200r roentgen irradiation on the level of the *eosinophils* in cats receiving folic acid and in cats held as controls (receiving no folic acid).

lated dose was 200r whole body radiation. As noted under Results, as well as in Tables 1, 2, and 3 and Figures 1, 2, 3, 4, and 5 no difference was found between the control and the experimental animals. The production of leukopenia by roentgen radiation was almost identical in the control and folic acid groups. Also the differential formulas were approximately the same in the two groups. No difference was detected in the response of animals in Group I and Group II—that is, the route of administration of folic acid did not alter the response to roentgen radiation.

It is difficult to understand how folic acid could protect against the effects of roentgen radiation. Exactly how radiant energy damages the function of

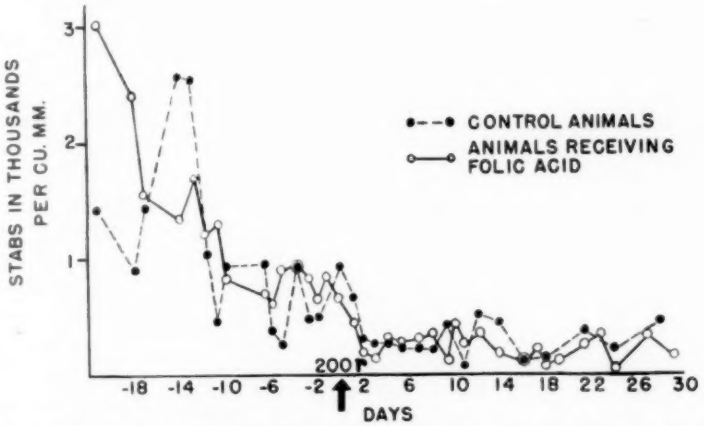

FIG. 5.—A comparison of the effect of 200r roentgen irradiation on the levels of the *stabs* (band forms) in cats receiving folic acid and in cats held as controls (receiving no folic acid).

TABLE 1.—CATS GIVEN ORAL AND SUBCUTANEOUS FOLIC ACID PRIOR TO AND FOLLOWING 200R WHOLE BODY ROENTGEN IRRADIATION

Cat Number	Average pre-irradiation WBC per cu. mm.	Average post-irradiation WBC per cu. mm. for week during maximum leukopenia	Maximum drop %	Average post-irradiation WBC per cu. mm. during entire period	Average drop %
1	12,160	3,933	67.7	4,003	67.1
2	29,103	5,825	80.0	8,140	72.0
3	14,672	5,150	64.9	5,522	62.4
4	23,606	6,058	74.3	6,334	73.2
5	15,825	5,783	63.5	7,072	55.3
6	14,353	4,350	69.7	4,650	67.6
Average	18,287	5,200	71.6	5,950	67.5

TABLE 2.—CATS GIVEN SUBCUTANEOUS FOLIC ACID PRIOR TO AND FOLLOWING 200R WHOLE BODY ROENTGEN IRRADIATION

Cat Number	Average pre-irradiation WBC per cu. mm.	Average post-irradiation WBC per cu. mm. for week during maximum leukopenia	Maximum drop %	Average post-irradiation WBC per cu. mm. during entire period	Average drop %
7	11,175	2,820	74.8	3,785	66.1
8	18,175	6,180	66.0	8,400	53.8
9	11,775	3,400	71.1	4,508	61.7
10	20,000	4,840	75.8	5,100	74.5
11	30,100	9,540	68.3	9,238	69.3
12	11,225	3,000	73.3	3,186	71.6
13	19,850	4,540	87.1	6,371	67.9
14	23,200	8,900	61.6	8,769	62.2
15	12,925	5,120	60.4	4,692	63.7
Average	17,603	5,371	69.5	6,005	65.9

hemopoiesis is not known, but whatever the mechanism, it is clear that folic acid does not protect against such damage. However, it should not be construed that these results are comparable to figures in which partial or regional roentgen treatment is employed. It is not inconceivable that some of the leukopenias which develop during the course of prolonged roentgen treatment, particularly of the thorax and abdomen, result from interference in the production, absorption, or utilization of substances such as folic acid by virtue of the effects of Roentgen-rays on the gastro-intestinal tract.

Summary. The prophylactic and therapeutic administration of folic acid to cats did not alter the occurrence or the magnitude of leukopenia caused by exposure to 200r whole body irradiation.

TABLE 3.—CATS GIVEN ONLY 200R WHOLE BODY ROENTGEN IRRADIATION AND *no* FOLIC ACID

Cat Number	Average pre-irradiation WBC per cu. mm.	Average post-irradiation WBC per cu. mm. for week during maximum leukopenia	Maximum drop %	Average post-irradiation WBC per cu. mm. during entire period	Average drop %
16	11,044	8,066	81.3	6,656	39.7
17	17,628	5,508	68.8	8,172	53.6
18	15,393	3,783	75.4	4,063	73.6
19	10,793	2,267	79.0	3,142	70.9
20	22,356	5,842	74.1	5,797	74.3
21	19,084	5,542	71.0	7,688	59.7
22	19,200	5,120	73.3	6,923	63.9
23	18,475	3,880	79.0	4,292	76.8
24	33,650	5,140	84.7	5,320	84.2
25	19,925	8,180	59.0	6,938	65.2
26	15,050	3,575	76.3	5,467	63.7
Average	18,436	5,173	74.7	5,860	68.4

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SEVERITY AND DURATION OF HYPERTENSION IN RELATION TO AMOUNT OF CARDIAC HYPERTROPHY*

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Hypertension, an accepted cause of cardiac hypertrophy, was mentioned by Bright[3] in 1836. Investigators of the relationship between duration and severity of hypertension on the one hand, and amount of cardiac hypertrophy on the other hand, however, have reached various conclusions.[6,7,18] In addition, studies more or less relevant to ours have had to do with the following: (1) the different effects on cardiac hypertrophy of malignant or mild hypertension[13]; (2) the onset of hypertension and the associated early fluctuant blood pressure[9,14]; (3) the effect of sex on the prognosis of hypertension[2]; (4) cardiac hypertrophy of rheumatic heart disease[10,19]; (5) the effect on cardiac hypertrophy of congestive failure or its absence in cases of coronary arteriosclerosis,[5] and, (6) the role of coronary sclerosis in the development of cardiac hypertrophy.[1,4,8,11,12,16] Our purpose here is primarily to add the results of our study to reports already printed.

Materials and method. Among the records of necropsies performed at the Mayo Clinic in the 6 years beginning with January 1, 1940, are 111 which represent cases in which normal readings of blood pressure had been obtained on one or more occasions but in which, nevertheless, hypertension subsequently had developed. As far as possible, records of cases in which valvular heart disease had existed were excluded.

Although the blood pressure and the severity of hypertension are not always closely related to the funduscopic changes, yet when record of the last mentioned findings was available, the severity of the hypertension was grouped[17] on the basis of them. When record of examinations of the ocular fundus was not available, the hypertension was grouped (except with reference to Group 4) according to arbitrary ranges of blood pressure. The lower limit of Group 2 was taken to be 200 millimeters of mercury systolic and 100 diastolic, and that for Group 3 was established as 240 systolic and 120 diastolic. Group 4 was recognized only if funduscopic examination had been performed.

To determine, from the records, how long hypertension had endured in each of the 111 cases was not entirely simple. Hypertension had ended, presumably, when the patient died, a date easily determined. When, however, had the hypertension begun? Patients had not been examined daily, of course. They had come to the clinic, had gone away and had returned. A long time might elapse between two successive examinations and it might be at some time in this interval that the hypertension had begun. Whether the condition had begun near the start or near the end of the interval could not be known. Therefore, the condition would have to be considered to have had its inception when the patient was examined for the last time before an interval of absence or when he was examined for the first time after an interval of absence. The former of these dates would be the start of a maximal period of hypertension; the latter, the start of a minimal period of hypertension. The maximal duration of hypertension in a given case, therefore, was considered to date from the last time that the patient had been seen at the clinic with the systolic or the diastolic blood pressure, or both, persistently less than 140/90. The minimal duration of hypertension, on the other hand, was considered to date from the first time that the systolic or the diastolic blood pressure, or both, were known to have risen to 140/90 or above. If hypertension of a

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lower group was succeeded by hypertension of a higher group, the duration of the disease was considered to be the sum of the duration of the hypertension of both groups. The average of maximal and of minimal duration has not been determined, for the quantities vary so widely that an average would not be reliable or significant.

In each instance, the heart had been weighed after the pericardium had been removed, the great vessels had been severed at their origins and the heart and great vessels had been opened and washed clean. What the normal weight of the heart would have been was calculated by multiplying the body weight of the patient by the appropriate factor as determined by H. L. Smith[15]. To exclude the possibility of a low estimate, and a consequently erroneous acceptance of the presence of hypertrophy, 20% was added to the calculated normal weight of the heart and the result was taken to be the calculated maximal normal weight of the heart. The hypertrophy was calculated as a percentage above this calculated maximal normal weight.

Observations. In the 111 cases reviewed (in which 65 of the patients were men and 46 were women) hypertrophy, in terms of the weight of the heart, varied from 0 to 176% more than the calculated normal. The average for the series was 46.8%.

The percentage of cardiac hypertrophy, when compared with the severity (group), and with the duration, of hypertension, gave some expected, and some unexpected, results. The percentage of hypertrophy appeared to be closely related to the severity (group) of the hypertension. Thus, in Table 1 it is demonstrated that the average percentage of hypertrophy was approximately twice as much in cases of hypertension of Group 4 as in cases of Group 1. On the other hand, no relationship appeared to exist between the percentage of cardiac hypertrophy and the duration of hypertension. These data are included in Tables 2 and 3. Except in hypertension of Group 4, moreover, no relationship could be observed between the severity (group) of the hypertension and its over-all duration; this is not shown in any of the tables published herewith. Five of the

TABLE 1.—THE PERCENTAGE OF CARDIAC HYPERTROPHY AND THE SEVERITY (GROUP) OF HYPERTENSION

Hypertrophy, %	Groups of hypertension: Group 1, cases	Group 2, cases	Group 3, cases	Group 4, cases	Total, cases
0-19	20	8	2	0	30
20-39	16	7	1	0	24
40-59	12	3	2	3	20
60-79	13	3	4	0	20
80-99	4	0	1	2	7
100-119	2	1	2	1	6
120-139	1	1	0	0	2
140+	1	0	0	1	2
Total, cases	69	23	12	7	111
Average hypertrophy, %	43.5	36.9	60.1	87.6	46.8

TABLE 2.—THE MINIMAL DURATION OF HYPERTENSION AND THE PERCENTAGE OF CARDIAC HYPERTROPHY

Hypertrophy, %	Minimal duration, years: 0-4	5-9	10-14	15-19	20-24	25+	Total, cases
0-19	13	4	5	3	4	1	30
20-39	8	4	3	1	2	6	24
40-59	8	5	2	5	0	0	20
60-79	5	2	4	6	1	2	20
80-99	2	4	0	0	0	1	7
100-119	3	0	1	0	1	1	6
120-139	1	1	0	0	0	0	2
140+	2	0	0	0	0	0	2
Total, cases	42	20	15	15	8	11	111
Average hypertrophy, %	48.9	51.4	38.1	47.6	36.0	48.2	46.8

7 patients whose hypertension had been of Group 4 had had severe glomerulonephritis, with a rapidly terminal course and consequent brief duration of the hypertension.

Once again, cardiac hypertrophy, when considered together with duration of hypertension, led to some impressions concerning the relative tolerance of persons of the two sexes to hypertension. In 6 of the 10 cases in which hypertrophy was greater than 100%, the patients were known to have had hypertension for less than 5 years. Of these 10 patients, 7 had been men. At necropsy, the weights of the hearts of only 4 patients in the series failed to exceed the normal, as determined by the criteria previously defined. In each of these 4 instances the patient was a woman. The minimal duration of hypertension in these 4 cases varied from 12 to 15 years. Moreover, in Table 4, it is evident that the percentage of males dwindled as the minimal duration of hypertension increased; the percentage of females, on the other hand, remained fairly constant. If it is considered that it was the hypertension which had caused death in these 111 cases, it seems that the women had withstood their hypertension better than the men.

Summary. In a series of 111 cases in which blood pressure once had been observed as normal but hypertension subsequently had developed, records of necropsy were reviewed. The percentage of cardiac hypertrophy appeared to be directly related to severity (group) of hypertension but unrelated to duration of hypertension. Moreover, except in hypertension of Group 4, relationship could not be found between severity (group) of hypertension and duration of hypertension. The women of the series seemed to have withstood their hypertension better than the men.

TABLE 3.—THE MAXIMAL DURATION OF HYPERTENSION AND THE PERCENTAGE OF CARDIAC HYPERTROPHY

Hypertrophy, %	Maximal duration, years							
	0-4	5-9	10-14	15-19	20-24	25+	Unknown	Total, cases
0-19	3	5	3	6	0	2	11	30
20-39	2	4	2	1	3	2	10	24
40-59	4	2	3	3	2	1	4	19
60-79	1	0	1	3	6	5	5	21
80-99	1	3	0	1	0	1	1	7
100-119	0	1	0	0	2	1	2	6
120-139	0	0	0	0	1	0	1	2
140+	1	0	1	0	0	0	0	2
Total, cases	12	15	10	14	14	12	34	111
Average hypertrophy, %	51.2	41.1	48.1	36.2	65.5	56.8	40.3	46.8

TABLE 4.—THE DISTRIBUTION ACCORDING TO SEX AND THE MINIMAL DURATION OF HYPERTENSION

Minimal duration, years	Males		Females		Total, cases
	Cases	%	Cases	%	
0-4	32	49.2	10	21.7	42
5-9	12	18.5	8	17.4	20
10-14	8	12.3	8	17.4	16
15-19	7	10.8	7	15.2	14
20-24	4	6.1	4	8.7	8
25+	2	3.1	9	19.6	11
Total	65	100.0	46	100.0	111

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A STUDY OF THE COMPARATIVE VALUE OF TETRAETHYLAMMONIUM BROMIDE AND DIAGNOSTIC SPINAL ANESTHESIA IN THE SELECTION OF HYPERTENSIVE PERSONS FOR SYMPATHECTOMY

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Some, but not all, persons with hypertension are benefited by extensive sympathectomy and ganglionectomy. However, there are as yet no reliable methods or tests by which one may with certainty distinguish those whose blood pressures will be favorably influenced from those whose pressure will not be significantly changed. Numerous rules and tests have been suggested for selecting persons suitable for operation. Smithwick[5] has laid down useful criteria which he has developed on the basis of his extensive experience. Essentially, these tests depend upon determining the effect on the blood pressure of sedation or sleep, which is assumed to minimize stimuli which affect the nervous system; or the effect of some method, such as the cold pressor test, which increases stimulation of the nervous system. By these methods one attempts to assess the neurogenic component of hypertension. These methods have not proved very satisfactory in the selection of patients for operation.

More recently 2 new tests have been proposed: the effect of tetraethylammonium ion and the effect of diagnostic spinal anesthesia. Each appears to have some merit but neither offers as yet the final solution.

Lyons[2] has proposed the use of the tetraethylammonium ion as a preoperative test for selecting hypertensive persons for sympathectomy and ganglionectomy. This test is based on the temporary blockade of the sympathetic ganglia so that the vaso-constricting action of the sympathetic nerves is abolished. Page[1], on the other hand, was unable to confirm this observation. He reported 12 cases. Five of his patients (Nos. 1, 4, 12, 14 and 15), as judged by our criteria, had no significant drop in diastolic pressure following the administration of tetraethylammonium chloride. Seven of his patients did have a significant drop in blood pressure following the administration of the drug. Two of these 7 patients were favorably influenced by lumbo-dorsal sympathectomy and ganglionectomy. Objections may be raised against his conclusions on the basis that the operative procedure was not sufficiently extensive.

Russek and his associates[4] have commented favorably on the effect of epidural anesthesia on the blood pressure as a test for the selection of hypertensive persons suitable for sympathectomy and ganglionectomy.

Because of the fragmentary work which had been done on the use of the tetraethylammonium ion and epidural anesthesia as tests for the selection of

hypertensive persons for sympathectomy, we thought it worth while to compare the blood pressure lowering effect of these two methods and to compare the effect of both of them with that obtained by an extensive thoracolumbar sympathectomy and ganglionectomy. Diagnostic spinal anesthesia was used in preference to epidural anesthesia because, in the opinion of Dr. Curtiss B. Hickcox, Professor of Anesthesiology at Temple University School of Medicine, it is technically easier and, with dilute solutions fractionally injected, sensory levels of anesthesia and autonomic block are easily obtained without the production of a motor block. This prevents muscular paralysis and relaxation and the consequent pooling of blood in the extremities which might further lower the blood pressure.

Methods and Materials. During 1947 and the first 2 months of 1948, 29 persons were admitted into Temple University Hospital for possible sympathectomy. Of these, 28 were tested for the blood pressure lowering effect of diagnostic spinal anesthesia. Twenty-five were tested for the blood pressure lowering effect of tetraethylammonium bromide. In 23 cases, both tests were applied. Of these in turn 20 came to operation and are the chief basis of this report.

The non-operative or incomplete cases include the following: 2 refused or were refused surgery. Two died after the first stage, 1 of a stroke and the other of heart failure. The first was a satisfactory risk who failed to react from anesthesia and at autopsy revealed necrosis of the right frontal parietal and temporal lobes. The second had malignant hypertension and was known to be an extremely poor operative risk. One refused the second stage. Two are to be done.

TABLE 1.—BLOOD PRESSURE DATA ON 24 HYPERTENSIVES:

(A) AVERAGE OF 10 SUPINE READINGS; (B) ONE SUPINE READING IMMEDIATELY BEFORE, AND (C) LOWEST SUPINE READING AFTER INJECTION OF 500 MGM. OF TETRAETHYLAMMONIUM BROMIDE

NAME AND CASE NUMBER	AGE	SEX	(A) AVERAGE BLOOD PRESSURE (10 READINGS) SUPINE	(B) PREINJECTION BLOOD PRESSURE SUPINE	(C) POST INJECTION BLOOD PRESSURE SUPINE	FALL IN THE SYSTOLIC PRESSURE (A–C)	FALL IN THE SYSTOLIC PRESSURE (B–C)	FALL IN THE DIASTOLIC PRESSURE (A–C)	FALL IN THE DIASTOLIC PRESSURE (B–C)
1 E.C.	33	F	226/151	240/150	140/100	86	100	51	50
2 P.B.	39	F	199/144	190/130	134/94	69	60	50	36
7 C.K.	26	F	159/117	192/130	148/108	11	44	11	22
8 R.D.	46	F	191/120	200/112	136/92	55	64	28	20
9 J.H.	41	M	179/107	180/110	140/90	39	40	17	20
10 M.R.	34	F	178/119	220/164	138/104	40	82	15	60
11 D.E.	24	F	196/143	234/164	174/140	22	60	3	24
12 A.V.	32	F	156/113	184/120	92/64	64	92	49	56
13 J.D.	41	F	171/104	200/110	110/70	71	90	34	40
14 M.K.	43	F	172/104	168/102	124/82	48	44	22	20
15 M.B.	49	M	208/132	240/140	160/88	48	80	44	52
16 A.S.	26	M	193/135	200/130	110/60	83	90	75	70
17 M.B.	45	M	219/130	242/148	212/130	7	30	0	18
18 C.O.	31	F	192/127	176/120	130/100	62	46	27	20
19 E.M.	50	F	203/128	170/110	104/66	99	66	62	44
21 C.P.	41	F	164/105	154/100	110/70	54	44	35	30
22 B.Y.	53	F	222/127	222/124	190/110	32	32	17	14
23 M.V.	38	M	201/133	194/110	126/88	75	68	45	22
24 I.K.	39	F	224/142	210/168	128/104	96	82	38	64
25 C.L.	48	F	215/133	230/140	182/110	33	48	23	30
26 C.G.	48	M	221/140	240/120	240/120	+ 19	0	20	0
27 C.G.	33	M	203/141	198/124	148/104	55	50	37	20
28 M.H.	47	F	154/99	170/110	128/84	26	42	15	26
29 M.S.	40	F	171/98	150/100	108/68	63	42	30	32

Two were tested following Smithwick operations done in 1945.

The remaining 20 were submitted to an extensive transpleural thoracolumbar sympathectomy bilaterally. Ganglia from the second thoracic to the second lumbar, inclusive, were resected along with the intervening chains and the splanchnic nerves down to but not including the coeliac ganglia. In 4 or 5 patients, the second and third thoracic or the second lumbar zones were not resected on one or the other side due to urgency for termination of the operation or the fact that the preoperative ascending diagnostic spinal test had indicated a drop of the blood pressure to normal at the level of the sixth thoracic segment or below. One had the malignant phase of hypertension, 13 had essential hypertension and 6 had mild to moderate impairment of renal function.

Blood pressure readings were taken in the supine, sitting and standing positions preoperatively and postoperatively to determine the effects of posture before and after operation, but only supine readings were taken following the administration of tetraethylammonium bromide and the use of diagnostic spinal anesthesia. All patients were in the hospital for at least one week and frequently for several weeks before operation. Blood pressure readings were taken twice daily by a trained nurse, checked frequently by a resident and taken repeatedly by at least one of us. Control values represent the average of the last 10 readings preoperatively. The postoperative values represent the average of the last 10 readings taken before discharge from the hospital. The blood pressure immediately preceding diagnostic spinal anesthesia and that preceding the administration of tetraethylammonium bromide are also given.

With the patient in bed, 500 mg. of tetraethylammonium bromide were injected intra-

TABLE 2.—BLOOD PRESSURE DATA ON 29 HYPERTENSIVES:

(A) AVERAGE OF 10 SUPINE READINGS; (B) ONE SUPINE READING IMMEDIATELY BEFORE, AND (C) LOWEST SUPINE READING AFTER DIAGNOSTIC SPINAL ANESTHESIA

NAME AND CASE NUMBER	AGE	SEX	(A) AVERAGE BLOOD PRESSURE (10 READINGS) SUPINE	(B) CONTROL BLOOD PRESSURE PRIOR TO SPINAL SUPINE	(C) MAXIMUM FALL IN BLOOD PRESSURE	FALL IN THE SYSTOLIC PRESSURE (A–B)	FALL IN THE SYSTOLIC PRESSURE (A–C)	FALL IN THE DIASTOLIC PRESSURE (A–B)	FALL IN THE DIASTOLIC PRESSURE (A–C)
1 E.G.	33	F	226/151	240/140	240/155	+ 14	0	+ 11	+ 15
2 P.B.	39	F	199/144	220/120	100/70	99	120	74	50
3 H.L.	28	F	215/117	200/110	150/80	65	50	37	30
4 A.L.	44	M	180/118	200/120	140/90	40	60	28	30
5 M.V.	42	F	195/112	230/130	90/60	105	140	52	70
6 M.S.	55	F	195/107	170/100	100/60	95	70	47	40
7 C.K.	26	F	159/117	205/110	120/75	39	85	42	35
8 R.D.	46	F	191/120	230/120	130/90	61	100	30	30
9 J.H.	41	M	179/107	160/105	108/74	71	52	33	31
11 D.F.	24	F	196/143	160/105	110/70	86	50	73	35
12 A.V.	32	F	156/113	160/120	110/80	46	50	33	40
13 J.D.	41	F	171/104	200/110	110/70	61	90	34	40
14 M.K.	43	F	172/104	194/110	125/85	47	69	19	25
15 M.B.	49	M	208/132	220/140	120/96	88	100	36	44
16 A.S.	26	M	193/135	220/140	130/110	63	90	25	30
17 M.B.	45	M	219/130	210/120	130/98	89	80	32	22
18 C.O.	31	F	192/127	184/120	130/80	62	54	47	40
19 E.M.	50	F	203/128	220/130	110/80	93	110	48	50
20 F.S.	40	F	187/118	200/140	140/92	47	60	26	48
21 C.P.	41	F	164/105	170/108	100/60	64	70	45	48
22 B.Y.	53	F	222/127	220/130	160/100	62	60	27	30
23 M.V.	38	M	201/133	230/150	160/110	41	70	23	40
24 I.K.	39	F	224/142	212/150	104/60	120	108	82	90
25 C.L.	48	F	215/133	240/130	160/100	55	80	33	30
26 C.G.	48	M	221/140	236/150	190/130	31	46	10	20
27 C.G.	33	M	203/141	190/144	170/118	32	20	23	26
28 M.H.	47	F	154/99	210/120	120/80	34	90	19	40
29 M.S.	40	F	171/98	190/90	150/90	21	40	8	0

venously and the blood pressure taken every minute for 5 minutes and then every 5 minutes until it reached its original level. The maximum drop in blood pressure is recorded (Table 1).

Diagnostic spinal anesthesia was performed by or under the direction of Dr. Hickcox. Continuous fractional spinal anesthesia was employed, with 0.2 to 2% of solution of procaine hydrochloride. The average dilution was 0.5%. If no reaction was obtained, the strength was decreased. The average fractional dose was 25 to 30 mg. of procaine hydrochloride. The pulse and blood pressure were checked at each sensory level for 4 to 5 minutes. Anesthesia was carried cephalad until the recumbent blood pressure dropped to normal and the level noted. In several, this required ascent to thoracic one and in 2 instances there was no decrease. The results are recorded in Table 2.

The operations were performed by one of us (WEB) or his associates. All operations, as previously described, consisted of extensive thoracolumbar sympathectomy and ganglionectomy. The postoperative results are recorded in Table 3.

Results. (a) Effects of tetraethylammonium bromide. The pharmacologic effects of the tetraethylammonium ion have been amply described previously and will not be repeated here. Two interesting phenomena not previously described or stressed were observed. One was a rise in blood pressure following the fall; this occurred in 3 of 20 cases, and on one occasion was 50 mm. of mercury higher than the pre-test level. This effect tended to occur about one-half hour after the maximum fall and lasted a few minutes. In the one with 50 mm. of mercury rise, a transient hemiparesis occurred. The other phenomenon was an apparent tolerance to the drug. In the beginning, we tried to treat our hypertensive patients with repeated injections of the drug. The injections were given at 4 hour intervals. There was less blood pressure lowering effect and the duration of the effect was shorter with succeeding doses. Only 3 patients were so tested and all 3 re-

TABLE 3.—BLOOD PRESSURE DATA ON 20 HYPERTENSIVES:

(A) AVERAGE OF 10 SUPINE PRE-OPERATIVE READINGS; (B) AVERAGE OF 10 SUPINE POST OPERATIVE READINGS FOLLOWING BILATERAL THORACOLUMBAR SYMPATHECTOMY

NAME AND CASE NUMBER	AGE	SEX	(A) AVERAGE PRE-OP BLOOD PRESSURE (10 READINGS) SUPINE	(B) AVERAGE MAXIMUM FALL IN BLOOD PRESSURE (10 READINGS) SUPINE	FALL IN THE SYSTOLIC BLOOD PRESSURE (A-B)	FALL IN THE DIASTOLIC BLOOD PRESSURE (A-B)
1 E.G.	33	F	226/151	154/106	72	45
2 P.B.	39	F	199/144	157/111	42	33
3 L.H.	28	F	215/117	185/109	30	8
4 A.L.	44	M	180/118	153/103	27	15
5 M.C.	42	F	195/112	146/92	49	20
6 M.S.	55	F	195/107	182/103	13	4
7 C.K.	26	F	159/117	162/112	3	5
8 M.D.	46	F	191/120	170/113	21	7
9 J.H.	41	M	179/107	149/97	30	10
10 M.R.	34	F	178/119	119/78	59	41
11 D.E.	24	F	196/143	206/146	10	3
12 A.V.	32	F	156/113	117/73	39	40
13 J.D.	41	F	171/104	135/93	36	11
14 M.K.	43	F	172/104	160/107	12	3
15 M.B.	49	M	208/132	139/91	69	41
16 A.S.	26	M	193/135	99/74	94	61
17 M.B.	45	M	219/130	222/149	3	19
18 C.O.	31	F	192/127	191/135	1	8
19 E.M.	50	F	203/128	138/85	65	43
20 F.S.	40	F	187/118	136/89	51	29

sponded to repeated injections of tetraethylammonium bromide in this way. These responses may represent inconstant effects of the drug or variable nervous tone in the patient rather than true tolerance. More observations are necessary to determine the nature of response to repeated injections at frequent intervals.

A significant drop in blood pressure was regarded as one in which the diastolic pressure fell 20 mm. of mercury or more compared to the average diastolic pressure. The drop in diastolic pressure compared to the pressure immediately preceding the test is also given, so that comparisons of the two drops can be made in order to determine what if any significance this drop has.

Eighteen of 24 had a significant drop in diastolic pressure following the administration of tetraethylammonium bromide. Eleven of 24 had a drop to normotensive levels. The nature, degree, duration, etiology of the hypertension or the sex had no relation to

TABLE 4.-DATA ON FALL OF DIASTOLIC BLOOD PRESSURE IN 29 HYPERTENSIVES:

EFFECTS PRODUCED BY (A) OPERATION, (B) DIAGNOSTIC SPINAL ANESTHESIA, AND (C) AFTER TETRAETHYLAMMONIUM BROMIDE INJECTION. (FIGURES REPRESENT FALL OF BLOOD PRESSURE IN MM/HG. A DASH SIGNIFIES THAT TEST OR OPERATION WAS NOT DONE).

NAME AND CASE NUMBER	AGE	SEX	(A) AFTER OPERATION	(B) AFTER DIAGNOSTIC SPINAL ANESTHESIA (B 1) COMPARED WITH AVERAGE OF 10 SUPINE READINGS	(B) AFTER DIAGNOSTIC SPINAL ANESTHESIA (B 2) COMPARED WITH A SUPINE READING JUST BEFORE ANESTHESIA	(C) AFTER TETRAETHYLAMMONIUM BROMIDE INJECTION (C 1) COMPARED WITH AVERAGE OF 10 SUPINE READINGS	(C) AFTER TETRAETHYLAMMONIUM BROMIDE INJECTION (C 2) COMPARED WITH A SUPINE READING JUST BEFORE THE DRUG INJECTION
1 E.G.	33	F	45	+ 11	+ 15	51	50
2 P.B.	39	F	33	74	50	50	36
3 H.L.	28	F	8	37	30	–	–
4 A.L.	44	M	15	28	30	–	–
5 M.C.	42	F	20	52	70	–	–
6 M.S.	55	F	4	47	40	–	–
7 C.K.	26	F	5	42	35	42	22
8 R.D.	46	F	7	30	30	28	20
9 J.H.	41	M	10	33	31	17	20
10 M.R.	34	F	41	–	–	15	60
11 D.E.	24	F	3	73	35	3	24
12 A.V.	32	F	40	33	40	49	56
13 J.D.	41	F	11	34	40	34	40
14 M.K.	43	F	3	19	25	22	20
15 M.B.	49	M	41	36	34	44	52
16 A.S.	26	M	61	25	30	75	70
17 M.B.	45	M	19	32	22	0	18
18 C.O.	31	F	8	47	40	27	20
19 E.M.	50	F	43	48	50	62	44
20 F.S.	40	F	29	26	48	–	–
21 C.P.	41	F	–	45	48	35	30
22 B.Y.	53	F	–	27	30	17	14
23 M.V.	38	M	–	23	40	45	22
24 I.K.	39	F	–	82	90	38	64
25 C.L.	48	F	–	33	30	23	30
26 C.G.	48	M	–	10	20	20	0
27 C.G.	33	M	–	23	26	37	20
28 W.H.	47	F	–	19	40	15	26
29 A.S.	40	F	–	8	0	30	32

the presence or absence of a significant drop in diastolic pressure.

Of the 24 tested with the drug, 15 were operated upon. Seven had significant drops in pressure postoperatively and 8 had poor results. Of the 7 good postoperative results, 6 had good responses to tetraethylammonium bromide and 1 had a poor response to the drug. Of the 8 bad postoperative results, 4 had good responses and 4 had poor responses to tetraethylammonium bromide.

(b) EFFECTS OF DIAGNOSTIC SPINAL ANESTHESIA. Twenty-three of 28 had a significant drop in diastolic pressure following spinal anesthesia. Twenty-one of 28 had a drop to normotensive levels. Again, the nature, degree, duration, etiology of the hypertension or the sex had no relation to the presence or absence of a significant drop in diastolic pressure.

Of the 28 tested with diagnostic spinal anesthesia, 19 were operated upon. Eight had significant drops in pressure postoperatively and 10 had poor results. Of the 8 good results, 7 had good responses to diagnostic spinal anesthesia and 1 had a poor response. Of the 10 bad results, 9 had good responses and 1 had a poor response to diagnostic spinal anesthesia.

Twenty-three patients were tested with both tetraethylammonium bromide and spinal anesthesia. Fourteen had good responses to both methods. Six had good responses to spinal anesthesia and poor responses to tetraethylammonium bromide, and 3 had poor responses to spinal anesthesia and good responses to tetraethylammonium bromide. Of the 14 patients who showed good response to both tests, 8 were subjected to operation. Four of these obtained good results and the other 4 were poor results.

Discussion. In Table 4 there are recorded the several effects produced in our 29 patients by both tests (when done) and operation (when performed).

It is generally recognized that during the first year after operation there is a gradual rise in pressure which is said to average somewhat less than 15 mm. of mercury diastolic. Our postoperative figures refer to the average of the last 10 pressures obtained before the patients left the hospital. Judged by some of our earlier patients, our results one year after operation will show less of a drop than as reported now. It was for this reason that 20 mm. of mercury was taken as the minimum significant drop. If the results are reported as a percentage of the diastolic pressure and 15% is regarded as significant, our findings are substantially the same.

Our findings verify the contention of Page and fail to verify the reports of Russek and the earlier report of Lyons. It can be seen that neither a significant response to tetraethylammonium bromide nor to diagnostic spinal anesthesia can be used to predict a satisfactory response to operation. Indeed, even a significant response to both procedures does not indicate that operation will be successful in lowering the diastolic pressure. The widespread effect of tetraethylammonium bromide on both the sympathetic and parasympathetic systems and the inconstancy of its effect on the same individual are probably some reasons for its failure as a reliable test to predict a satisfactory outcome from surgery. The frequency with which diagnostic spinal anesthesia can produce drops in pressure to normotensive levels suggests that additional mechanisms are in action which are not present after operation.

A comparison of the blood pressure lowering effects of spinal anesthesia and tetraethylammonium bromide shows that in more than half the patients both procedures produced

significant changes in pressure. In a little less than half, one procedure produced an adequate response and the other did not. In some instances, spinal anesthesia was superior to tetraethylammonium bromide in its blood pressure lowering effects and in others the reverse was true. Likewise, the degree of reaction was frequently different. This indicates that these procedures affect different factors which together are responsible for the maintenance of blood pressure.

More recently, Lyons[3], on the basis of more evidence, has come to a conclusion similar to ours so far as the tetraethylammonium ion is concerned. He states that "a good response to the drug does not necessarily indicate that a successful result from splanchnicotomy can be expected." He rather cautiously suggests that the failure of response to the drug may be used as a test to exclude hypertensive persons for splanchnicotomy. The same thought with regard to epidural anesthesia is implied in the work of Russek.

It can be seen from our findings that one patient with a poor response to diagnostic spinal anesthesia and one patient with a poor response to tetraethylammonium bromide had excellent results following operation. Furthermore, the blood pressure of the patient varies from time to time and the response of the patient to tetraethylammonium bromide varies from time to time. Two extreme conditions may be obtained: The pre-test blood pressure may be higher or lower than the average blood pressure. In the first instance, a marked response to the drug may occur without having the resultant pressure lower than the average pressure. In the second instance, no response from the drug may occur because the pressure has already dropped considerably compared to the average pressure. This is seen in Cases 17 and 26. Furthermore, because of the great variability of the pressure, one is never certain of the true average pressure from a short period of observation. Lastly, the neutralizing effect of an increase in adrenalin cannot be excluded. For these reasons, with the data available at the present time, we feel it unwise to exclude patients from operation simply on the basis of poor responses to those two tests.

Because of the failure of these tests to predict accurately the outcome of surgery we re-examined our clinical findings to see whether one of the usual rules given for selection of patients for sympathectomy could have been applied successfully. Our group was relatively young. No patient was above the age of 50. Two out of 5 males and 7 out of 15 females obtained significant postoperative decrease in diastolic pressure. The pulse pressure was less than 19 plus one-half the diastolic pressure in all persons whose operation was successful (Types I and II of Smithwick). However, 7 persons whose operation was unsuccessful had similar pulse pressures. Therefore this criterion was no more reliable.

Summary and Conclusions. 1. Of 29 hypertensive persons admitted for possible sympathectomy and ganglionectomy, 28 were tested for the blood pressure lowering effect of fractional spinal anesthesia, 24 were tested for the blood pressure lowering effect of tetraethylammonium bromide and 20 were subjected to an extensive bilateral thoracolumbar sympathectomy and ganglionectomy.

2. The inconstancy of the blood pressure lowering effect of tetraethylammonium bromide is stressed.

3. Eighteen of 24 had good responses to tetraethylammonium bromide. Twenty-three of 28 had good responses to diagnostic spinal anesthesia. Fourteen of 23 had good responses to both tests.

4. Seven good responses to sympath-

ectomy had 6 good responses and 1 bad response to tetraethylammonium bromide. Eight bad results of operation had 4 good and 4 bad responses to the drug.

5. Eight good results of sympathectomy had 7 good responses and 1 bad response to diagnostic spinal anesthesia. Ten bad results of operation had 9 good responses and 1 bad response to diagnostic spinal anesthesia.

6. Eight good responses to both tetraethylammonium bromide and spinal anesthesia obtained 4 good results and 4 poor results from operation.

7. Good responses from tetraethylammonium bromide or diagnostic spinal anesthesia or from both can not be used as reliable tests to predict good results from sympathectomy.

8. With our present data, it is advised that sympathectomy should not be withheld on the basis of insignificant responses to tetraethylammonium bromide or spinal anesthesia.

9. A re-examination of our clinical data fails to reveal any method, including the pulse pressure, which will predict accurately the blood pressure lowering effect of sympathectomy.

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ELECTROCARDIOGRAPHIC AND CLINICAL STUDIES ON THE ACTION OF ERGOTAMINE TARTRATE AND DIHYDRO-ERGOTAMINE 45

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In recent years preparations of ergotamine have been used rather widely in cardiovascular research and have been advocated for the treatment of various conditions. Thus, they have been administered for the treatment of hypertension[10] and paroxysmal tachycardia.[4] Moreover, ergotamine has been recommended as a diagnostic test in subclinical rheumatic fever,[18] and on the basis of animal experimentation, it has been suggested that the administration of ergotamine may reduce the immediate mortality in acute coronary occlusion.[9]

The view has been expressed that a high sympathetic tonus is responsible for the abnormal T waves often seen when individuals assume the erect posture. This opinion is based on the observation that the intravenous injection of ergotamine tartrate prevents the appearance of these electrocardiographic changes.[11] Likewise, alterations of the T waves in the chest leads have been ascribed to "functional" influences produced by an abnormal vagus or sympathetic tonus. Following the intravenous injection of 0.5 mg. of ergotamine tartrate these alterations of the T waves disappeared and were explained by excessive adrenergic preponderance.[7,11,15,17,19]

Finally during the anoxemia test abnormal electrocardiographic changes occasionally occur in patients with healthy hearts. If the anoxemia test is repeated after the administration of ergotamine, these changes were said to be absent; this permits one to differentiate between the alterations due to organic coronary disease and those found in patients with normal coronary arteries.[1,3]

In a previous study it was demonstrated that changes in the electrocardiogram which occur on standing are occasionally but not always prevented by ergotamine.[13] Deep inversion of the T waves may appear on assuming the erect posture even after the injection of ergotamine.

It seemed to us that if ergotamine preparations could change the repolarization process and alter the functionally inverted T waves by their sympathicolytic action they should also have a similar effect in organic heart disease and occasionally lead to a normalization of organically inverted T waves.

Method of study and material. Nineteen patients who suffered from organic heart disease and who showed inverted T waves in leads I and CF_5 were studied. These T wave changes were caused by left ventricular hypertrophy in luetic heart disease, rheumatic heart disease, hypertension or by an old myocardial infarction.

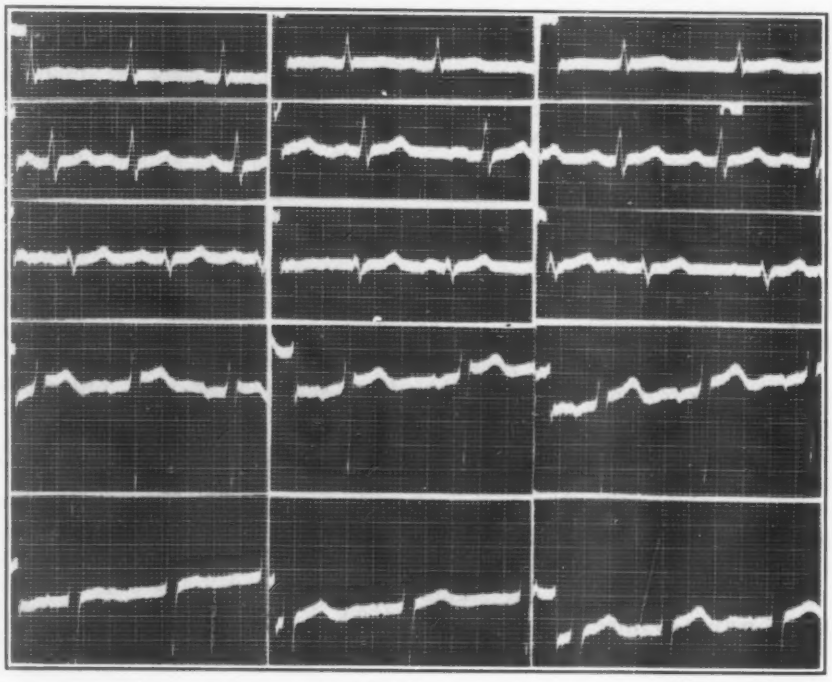
All electrocardiograms were obtained with the patient in the supine position. The

patient received an intravenous injection of 0.5 mg. of either ergotamine tartrate or dihydro-ergotamine 45* after the recording of the control electrocardiogram. Electrocardiograms were then taken 15, 30 and 45 minutes after the injection.

Results. Seven of the 19 patients developed significant alterations of the T waves after the administration of ergotamine. As Table 1 shows, the inverted T_1 became upright in 4 patients and the inverted T waves in Lead CF_5 became upright in 3 instances. In 2 patients the originally inverted T waves in Lead I became more inverted and a similar phenomenon occurred twice in Lead CF_5.

Figure 1 shows the electrocardiogram of a 59 year-old male patient who had a history of hypertension and cardiac decompensation for a number of years. The control electrocardiogram (Fig. 1a) shows a slight left axis deviation, some slurring of the QRS complexes and flat T waves in Leads I and CF_5. Fifteen minutes after the injection of ergotamine tartrate the T waves have become higher (Fig. 1b) and they are almost normal 45 minutes after the injection (Fig. 1c).

Figure 2 shows the electrocardiogram of a 56 year-old man with a blood pressure of 210/130 mm. Hg. The heart was markedly enlarged and there was evidence of right and left ventricular failure. Figure 2a shows Lead I and CF_5 with a depression of the RS-T segments and inverted T waves, as is often seen in long lasting hypertension with left ventricular hypertrophy. Fifteen minutes after the injection of 0.5 mg. of ergotamine tartrate there are no significant changes in Lead I but positive T waves appear in Lead CF_5



A B C

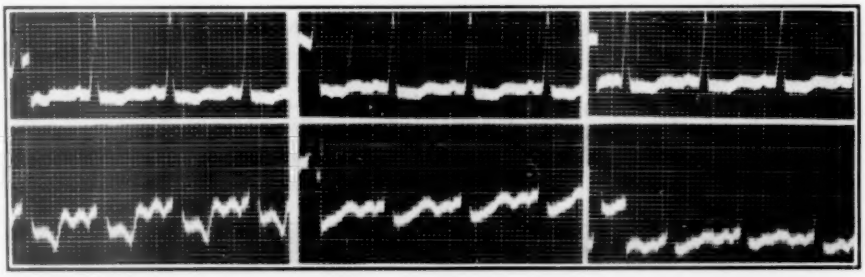
Fig. 1.—Fig. 1a shows the electrocardiogram before, and Fig. 1b 15 minutes after the intravenous injection of ergotamine tartrate. Fig. 1c was obtained 45 minutes after the injection. The 2 bottom tracings are Leads CF_2 and CF_5.

* Our thanks are due to Dr. Henze of the Sandoz Company for the supply of this drug.

(Fig. 2b). These changes still persist 45 minutes after the injection (Fig. 2c).

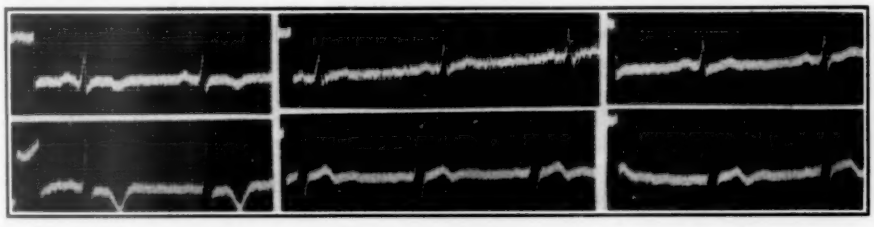
It is evident from these results that not only functionally inverted T waves but also T waves which are inverted because of organic heart disease may become upright following administration of ergotamine.

Anginal pain following ergotamine. Five of the patients developed severe anginal pain after the injection of ergotamine and one of these patients died during the attack.



A B C

Fig. 2.—Fig. 2a shows Lead I and Lead CF_5 before, and Fig. 2b and 2c, 15 and 45 minutes after the intravenous injection of ergotamine tartrate.



A B C

Fig. 3.—Fig. 3a was recorded before the intravenous injection of dihydro-ergotamine 45 and Figs. 3b and 3c were obtained respectively 15 and 45 minutes after the injection.

Case Reports: *Case 1.* A 75 year-old male had a history of coronary thrombosis 2 years before admission. The patient was hospitalized because of angina on effort which had become progressively worse. Figure 3a shows the electrocardiogram (Leads I and CF_5) taken before the administration of ergotamine. It shows normal RS-T segments and deeply inverted T waves. These findings are consistent with an old infarction of the anterior wall of the left ventricle. Fifteen (Fig. 3b) and 45 minutes (Fig. 3c) after the intravenous injection of dihydro-ergotamine 45 the T waves were distinctly positive in both Lead I and Lead CF_5.

Within 5 minutes after the injection the patient complained of excruciating pain which was similar to the angina he experienced on effort. This present pain however was more severe. The pain persisted for 10 hours and because of this and marked sweating, retching and vomiting a fresh coronary thrombosis was suspected. The subsequent findings did not show evidence of a new myocardial infarction and an electrocardiogram taken 4 hours after the onset of the pain but while pain still persisted, showed a pattern similar to that in Figure 3a. Subsequent electrocardiograms revealed no further changes.

Case 2. A 75 year-old male had a hypertension for many years and was admitted to the hospital because of left ventricular failure. The electrocardiogram showed depression of the RS-T segments

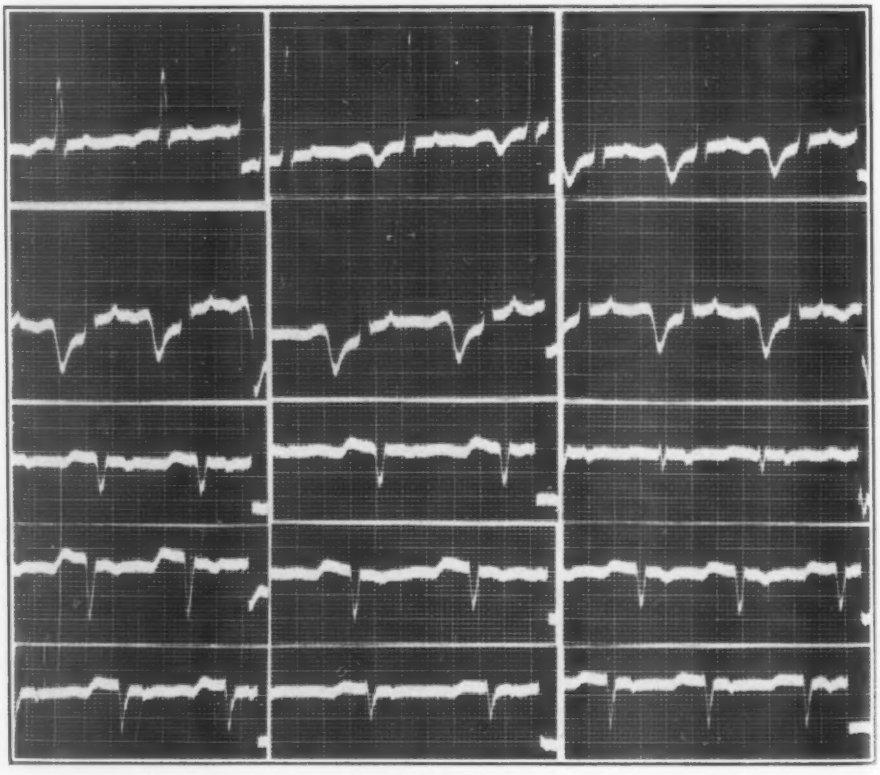
and low T waves in Leads I and CF_5. The other leads were normal. Fifteen minutes after the injection of dihydro-ergotamine 45 the T waves in the apical chest lead became deeply inverted. The inversion increased during the next 15 minutes but subsided somewhat after 45 minutes. The T waves in Lead I were isoelectric 30 and 45 minutes after the injection. No changes developed in the other leads.

This patient developed severe substernal pain, profuse sweating, nausea and tingling in the extremities within 10 minutes after the injection. The substernal pain persisted for 2 hours.

Case 3. A 65 year-old male who was admitted because of left ventricular failure and with a blood pressure of 190/100. The electrocardiogram showed a typical pattern of left ventricular strain. This patient developed substernal pain 10 minutes after the injection of 0.5 mg. of ergotamine tartrate and this pain persisted for one hour. Electrocardiograms taken 15, 30 and 45 minutes after the injection showed no change from his control tracing.

Case 4. A 63 year-old male was admitted to the hospital for left ventricular failure with a blood pressure of 220/130. He also showed an electrocardiographic pattern of left ventricular strain. Anginal pain occurred 15 minutes after the injection of ergotamine tartrate and lasted for 45 minutes. No alterations occurred in the electrocardiogram.

Case 5. Figure 4 shows the tracings from a 58 year-old male with syphilitic heart disease, incompetency of the aortic valves and stenosis of the coronary ostia. As this patient died following the injection of 0.5 mg. of dihydro-ergotamine 45,



A B C

Fig. 4.—Fig. 4a shows the 3 standard leads and Leads CF_4 and CF_5 before the intravenous injection of dihydro-ergotamine. Fig. 4b was taken 15 minutes after the injection and Fig. 4c 30 minutes later.

the observations will be reported in greater detail.

The patient was in good health until 2 years before admission when weakness, shortness of breath, malleolar edema and retrosternal pain on exertion developed. For the past 2 months substernal pain appeared on the slightest exertion but subsided with rest. Several years ago the patient was told that he had a hypertension. He denied lues but admitted to an urethral stricture. The family history revealed that 2 brothers had died from heart disease and the mother from a stroke.

The patient was in no acute distress on admission. The eyes reacted poorly to light; there was ataxia of the hands and the legs, and diminished vibratory sense over the right lower extremity. The carotid pulsations were forceful and equal and the cervical veins were distended. There was a water hammer pulse and the blood pressure was 150/45. The apex was in the 6th intercostal space outside of the mid-clavicular line; the heart of an aortic shape with a marked dilatation of the left ventricle and a widening of the ascending aorta. Systolic and diastolic murmurs were heard over the right second intercostal space. There was some fluid in the right pleural sinus. The liver was markedly enlarged and there was pitting edema of the ankles.

The patient improved with therapy. On the 6th day after admission at 10 A.M., the patient was given an intravenous injection of 0.5 mg. of dihydro-ergotamine 45. Ten minutes later he complained of severe substernal pain, was very nauseated, dyspneic and insisted upon sitting up in bed. At noon the pain still persisted and it was noted that the patient was incoherent, cold, clammy and vomiting. At 4 P.M., pain was still present, the cardiac rate was 128 per minute with many extrasystoles. The respiration was rapid and irregular. The blood pressure which had been 160/50 one half-hour previously was now 110/50. At 8 P. M. the pain still persisted, the blood pressure was 115/55 and the heart rate had slowed to 84 per minute. The patient seemed more alert. He died at 9:50 P.M.

The autopsy revealed syphilitic aortitis with aortic insufficiency, atheromatosis, narrowing of both coronary orifices and coronary sclerosis. The left ventricle was hypertrophied and myocardial fibrosis was present in the apical area. Pulmonary edema and chronic congestion of the liver existed.

The electrocardiogram taken before the injection (Fig. 4a) showed slurring but no widening of the QRS complexes and inverted T waves in the limb leads. Only equivocal modifications of the T waves appeared 15 minutes after the injection (Fig. 4b). These were accompanied by slight changes of the QRS complex. In the tracing taken 45 minutes after the injection, the inversion of the T waves in the limb leads was more marked and the T waves in Lead CF_5 became abnormal (Fig. 4c).

Discussion. This investigation shows that alterations of the electrocardiogram which are due to organic heart disease may disappear with the administration of ergotamine preparations. As Table 1 indicates, this normalization of the inverted T waves in patients with organic heart disease is seen in many different conditions and not only in patients with hypertension.

Preparations of ergotamine do not produce a consistent alteration of organically inverted T waves. Table 1 shows that in 12 patients no changes of the T waves occurred. Of the 7 patients who developed significant changes, in 2 the inverted T waves became even more inverted and in 5 normalization of the previously inverted T waves occurred. Further investigation will be necessary to explain these differences of response.

All of the changes which occur in the electrocardiogram after the administration of ergotamine preparations can not be attributed to the sympathicolytic properties of this drug. It has been shown that the accelerans mechanism in the heart is not paralyzed by ergotamine even when huge doses are given.[12] The effect of the drug on the blood pressure in man is variable and often slight. A direct vasoconstricting action

of the coronary arteries is probable.[14]

Five of the patients studied developed severe substernal pain after the injections of ergotamine and one of these patients died. The electrocardiographic changes did not parallel the symptom of angina. Two of the patients who had anginal pain did not show any change in the electrocardiogram and the patient who died during a severe anginal attack developed the electrocardiographic change after 45 minutes, long after the pain had appeared. One patient had a normalization of the electrocardiogram in spite of severe anginal pain (Fig. 3). This same lack of parallelism exists in spontaneous attacks of exertional angina and in attacks induced by the exercise test.

Anginal pain and cardiac complications following the administration of ergotamine have been previously reported. Severe anginal pain occurred in a 49 year-old woman with an exophthalmic goiter after each of the 3 intramuscular injections of 0.5 mg. of ergotamine tartrate. Amyl nitrite did not bring relief and morphine had to be given.[5] The same author observed a death a few hours after the administration of ergotamine in a 60 year-old woman with hyperthyroidism.[6] Similar to our own case with the same unfortunate outcome was another observation.[20] A 43 year-old woman with an aortic regurgitation and angina on effort, developed a severe attack of angina pectoris after the administra-

TABLE 1. THE EFFECT OF ERGOTAMINE PREPARATIONS ON ORGANICALLY INVERTED T WAVES

				15 minutes		*30 minutes*		*45 minutes*		
Name	*Age*	*Diagnosis*	*Medication*	T_1	T_{CF_5}	T_1	T_{CF_5}	T_1	T_{CF_5}	*Reactions*
J.Y.	45	Rheumatic heart	Gynergen	I to U	O	I to U	O	I to U	O	none
C.I.	59	Left vent hypertrophy	Gynergen	I to U	I to U	I to U	I to U	I to U	I to U	none
F.S	55	Rheumatic heart	DHE 45	O	I to −I	O	I to U	O	I to U	nausea vomiting
J.P.	75	Coronary thrombosis	DHE 45	I to U	I to U	I to U	I to U	I to U	I to U	angina for 10 hours
G.R.	75	Left vent. hypertrophy	DHE 45	I to +I	I to +I	I to +I	I to +I	I to +I	I to +I	angina for 2 hours
J.K.	56	Left vent. hypertrophy	Gynergen	O	I to U	O	I to U	O	I to U	none
E.M.	58	Leutic heart	DHE 45	O	U to −U	O	U to −U	I to +I	U to −U	angina, died
J.C.	65	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	angina
A.F.	65	Left vent. hypertrophy	DHE 45	O	O	O	O	O	O	nausea vomiting
G.D.	60	Left vent. hypertrophy	DHE 45	O	O	O	O	O	O	none
A.A.	44	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
A.K.	48	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	nausea
A.S.	60	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
J.C.	63	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	angina
S.L.	35	Rheumatic heart	Gynergen	O	O	O	O	O	O	tingling in legs
R.S	45	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
C.R.	59	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
C.S.	46	Old coronary thrombosis	Gynergen	O	O	O	O	O	O	none
S.G.	39	Rheumatic heart	Gynergen	O	O	O	O	O	O	nausea vomiting

LEGEND:
I to U = inverted to upright
O = no change
U to +U = increase in the uprighting
U to −U = decrease in the uprighting
I to −I = inverted to less inversion
I to +I = inverted to greater inversion

tion of 1 mg. of ergotamine tartrate. Nitroglycerine did not relieve. The pain gradually increased in intensity and the patient died 24 hours after the injection. During this period there was a depression of the RS-T segments in Leads I and II similar to that observed during her spontaneous attacks of angina pectoris. The post mortem examination revealed a syphilitic aortitis, insufficiency of the aortic valves and a marked stenosis of the coronary ostia.

Lichtman reported 3 patients with anginal pain after the oral administration of ergotamine tartrate.[8] One was a 65 year-old man with advanced generalized arteriosclerosis who developed tachycardia, precordial distress and a fall of blood pressure after the oral dose of 1 mg. of ergotamine. Carter reported a woman with migraine who developed immediate palpitation, tachycardia and substernal pain after the intramuscular injection of 0.5 mg. of ergotamine tartrate.[2] Three hours later auricular fibrillation occurred which reverted to normal sinus rhythm at 5 hours but the substernal pain persisted for 9 hours. Repeated electrocardiograms were normal.

In view of our experiences and the reports in the literature, the employment of ergotamine and its derivatives as has been recently suggested in patients with coronary disease is hazardous and should be avoided. Coronary artery disease is a contraindication for these drugs.[16]

We are not able to explain the long duration of the untoward effects of ergotamine nor can we conclude whether only those patients with coronary artery disease will show these toxic reactions, or whether these effects may occur in patients with normal coronary vessels. Our investigations were terminated because of the death of the last patient to whom we administered ergotamine.

Conclusions. Ergotamine preparations cannot be used to differentiate the functionally inverted T waves from those which are inverted because of organic heart disease; temporary normalization of the inverted T waves may occur in both conditions after administration of ergotamine.

The use of ergotamine preparations in patients with coronary artery disease, is hazardous.

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THE USE OF QUINIDINE SULPHATE IN THE TREATMENT OF HICCUP, A PRELIMINARY REPORT

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This report is based on our experience in the use of quinidine sulphate in the treatment of 9 cases of persistent hiccup, in 6 of which the drug proved effective (Cases 1, 3, 5, 6, 8, 9). In 2 patients (Cases 2, 4) the hiccup was improved but did not stop altogether, and in 1 (Case 7) this treatment was apparently of no help.

Hiccup has been described as an intermittent clonic contraction of the diaphragm often associated with clonic contraction of the accessory muscles of respiration, or as a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis. It is due to a great variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord, the centers themselves or their efferent pathways to the muscles. Reflexes through the vagus may play a part in its production. Kremer[12] (1922) was of the opinion that the clonic contraction of the diaphragm is set off by an irritation of the respiratory center. This can be initiated by: (*a*) disturbance in the central nervous system; (*b*) a chemical irritation resulting from anoxemia, uremia, and toxic products; and (*c*) by stimulation of the sensory fibers of the phrenic and sympathetic nerves and also by reflexes through the peripheral nerves.

A multitude of conditions may incite the attacks, such as a diseased state in the abdomen, chest or brain, and systemic infections as well as psychologic factors. Among the frequent conditions which precipitate these seizures are disorders of the esophagus and stomach, such as gastritis and gastric dilatation, intestinal obstruction, ileus, strangulated hernia, acute appendicitis, acute pancreatitis, peritonitis, renal disease with azotemia, liver disease, tumors and inflammatory disease of the mediastinum, disease of the heart and pericardium, brain tumor, meningoencephalitis, epidemic encephalitis, cerebrovascular accident, typhoid fever, and other severe infections.

The methods of treatment are numerous. Among the procedures commonly mentioned are: pressure upon the phrenic nerve between the heads of the sternocleidomastoid muscle, drinking cold water, holding the breath, or the induction of sudden fright. Gastric lavage will often give relief when irritation of the gastric mucous membrane is present. Apomorphine, gr. $\frac{1}{8}$ hypodermically, or hyoscine hydrobromide, gr. $\frac{1}{200}$, may be given and repeated after 3 hours. Morphine by itself rarely succeeds in stopping an attack. Benzyl benzoate ($\frac{1}{2}$ dram of a 20% solution) sometimes stops the attacks. Inhalations of amyl nitrite and chloroform have been used. Application of an ice bag to the neck, ethyl chloride sprayed on the epigastrium, repeated traction of the tongue, pressure on the eyeballs, mechanical dilatation of the esophagus, and pressure upon the ribs near the origin of the diaphragm, have all been tried. Inhalation of 5 to 10% carbon dioxide in oxygen may be pursued until the patient has had an

absence of hiccup for a 1 minute period. If hiccup recurs, as it often does, inhalation of carbon dioxide should be begun again. In intractable cases, Weeks[18] (1931) suggested that the patient should be examined fluoroscopically to determine the side of the diaphragm involved. The phrenic nerve on the affected side is then exposed and anesthetized; crushing or avulsion may be required to stop the attack. Occasionally bilateral phrenicotomy has been performed (Campbell[4], 1940). The pros and cons of this method should be carefully considered before it is used. This procedure results in decreased pulmonary ventilation on the affected side and may further embarrass an already impaired cardiovascular system.

Following the failure of the usual methods to stop an attack of hiccup in a patient who was becoming rapidly exhausted (Case 1), for reasons mentioned later, the use of quinidine was suggested by one of us. In view of the recent experience that more beneficial effects were obtained by the use of large doses in the treatment of ventricular tachycardia, a similar regimen was pursued in this patient. As far as we know this procedure has not been used previously in the treatment of hiccup.

Short histories of our 9 cases follow:

Case Reports. Case 1. A. B., a white man, 75 years of age, poorly nourished, was admitted to the hospital on June 23, 1947. He had suffered 3 previous attacks of myocardial infarction, but had had no recent cardiac episodes. Hiccup had been present for 10 days and was refractory to the usual treatment at home. His general condition was poor. Moderate dyspnea was present. The heart sounds were of poor quality and the normal cardiac rhythm was interrupted by frequent extrasystoles. He had been taking digitalis for several years and was adequately digitalized. An electrocardiograph showed evidence of myocardial damage and digitalis effects. Treatment in the hospital for the hiccup with oxygen, carbon dioxide, alcohol intravenously, ether rectally, and the usual sedatives and antispasmodics was unsuccessful in relieving the hiccup. The patient was rapidly becoming weaker. On the 4th hospital day (after 14 days of hiccuping) 10 grains of quinidine sulphate were administered by mouth and within one-half hour the hiccup ceased, but recurred in 2 hours. Two successive doses of 10 grains of quinidine sulphate given 1 hour apart relieved the hiccup for 8 hours. Ten grains of quinidine sulphate again relieved the hiccup for 12 hours. The same dose of quinidine was repeated and the hiccup did not recur.

A total of 50 grains of quinidine sulphate was administered in a period of 2 days. Response to each dose was noted within about 2 hours. The extrasystoles were completely eliminated and a slight increase in the intraventricular conduction time was noted. The patient was discharged on the 11th hospital day, markedly improved.

Case 2. L. B., a colored man, 67 years of age, was admitted to the medical wards with a diagnosis of prerenal azotemia secondary to diarrhea and hematemesis. The blood urea nitrogen was 137 mg. per 100 cc. and the carbon dioxide combining power was 27 volumes per cent. Roentgen ray of the chest revealed evidence of bilateral caseous tuberculosis. He had had hiccup continually for 72 hours. Following the administration of 9 grains of quinidine sulphate intramuscularly, the hiccup ceased 30 minutes after the injection but recurred in 2 hours. A small dose of quinidine was again administered. The hiccup stopped 15 minutes but recurred in 2 hours. He was given 5 grains of quinidine by mouth every 3 hours for 3 doses. The hiccup stopped 1 hour after the 1st dose. On the following day, quinidine sulphate, grains 9 intramuscularly, was again given for an attack of hiccup. It stopped in about 10 minutes and he was relieved for 2 hours. A similar dose was again given and the hiccup promptly disappeared. He was then placed on a maintenance dose of quinidine, 6 grains every 3 hours, orally, for the next 18 hours. During the latter part of each 3 hour period the hiccup recurred. In the next 3 days he had several short attacks of hiccup which were not considered to be of sufficient length to require therapy. The patient died 3 days later with azotemia and terminal bronchopneumonia.

Comment. The results of quinidine administered for hiccup in this case seem to indicate that 9 grains given intramuscularly were effective in stopping the hiccup. However, this effect was only temporary

and lasted about 2 hours. The oral administration of 6 grains every 3 hours as a maintenance dose was only partially effective in controlling the hiccup.

CASE 3. W. B., a negro 60 years of age, was admitted to the hospital with a diagnosis of adenocarcinoma of the prostate. He was found to have uremia secondary to a bilateral pyelonephritis. The blood urea nitrogen was 150 mg. per 100 cc. He had been hiccuping continually for 4 days and had received no relief from the usual measures.

On July 27, 1947, at 11 A.M., 9 grains of quinidine sulphate were given intramuscularly. At 1:10 P.M., it was noted that the frequency of hiccup had been reduced in rate. He was then given quinidine sulphate, 9 grains, orally; this was repeated in 2 hours. At 5:30 P.M., the hiccup ceased but recurred at 10 P.M.

On July 28, 1947, at 11:30 A.M., the patient was given 9 grains of quinidine intramuscularly and at 1:30 P.M. his hiccup was relieved. He had no recurrence of singultus after this time. This patient died in azotemia 1 week later but had no recurrence of the hiccup.

CASE 4. W. B., a negro 52 years of age, was admitted to the hospital with a diagnosis of intestinal obstruction. Operation revealed many adhesions between the transverse colon and anterior parietal peritoneum. Postoperatively he developed atelectasis with bronchopneumonia. Following the operation, hiccup developed and continued intermittently for 3 days. Ethyl chloride sprayed upon the abdomen and chest and the inhalation of amyl nitrite failed to relieve the hiccup. On July 28, 1947, the 3d postoperative day, he received 9 grains of quinidine intramuscularly at 5:35 P.M., and 9 grains intramuscularly at 6:35 P.M. The singultus stopped 10 minutes following the 2d dose. Similar doses of quinidine were given at 7:35 P.M. and 9:30 P.M. The hiccup remained quiescent until 12 P.M., at which time he received another intramuscular injection of the same amount of quinidine. The hiccup was again arrested within 15 minutes from the time of administration and remained so for 22 hours. At 3 A.M., another attack stopped about 10 minutes after the injection. No evidence of hiccuping was encountered after this time until the following afternon. Because the patient was vomiting and since none of the intramuscular preparation was available, he was given 10 grains of quinidine dissolved in 20 cc. of normal saline solution by the intravenous route. Following the injection the hiccup decreased in frequency from 35 to 18 per minute, and a diminution in depth was noted. The hiccup did not stop immediately but was gone about 2 hours later. These attacks did not recur during the remainder of his stay in the hospital (6 days).

The patient was discharged to the surgical clinic.

CASE 5. V. R., a negro, 46 years of age, was admitted to the genito-urinary department with a diagnosis of urinary extravasation, secondary to a gonorrheal urethral stricture. The blood urea nitrogen was 29 mg. per 100 cc., and the carbon dioxide combining power was 37 volumes per cent. The patient had experienced hiccup intermittently for 48 hours and continuously for 12 hours previous to treatment. Quinidine sulphate, 9 grains, was administered intramuscularly at 2 P.M., and every hour thereafter for 3 hours. The hiccup gradually decreased in frequency and stopped 4 hours after the last dose was given. He had received no other medication for the treatment of hiccup.

The patient experienced short mild episodes of hiccuping the following day, which ceased without medication. He had no recurrence of singultus for the next week of his hospital stay. He was then discharged to the genito-urinary clinic.

CASE 6. A. B., a negro, 35 years of age, was admitted to the orthopedic ward with a diagnosis of Pott's disease and tuberculosis of the mediastinum. On admission the temperature was 103° F., pu'se 120, and respirations were 30 per minute. The patient had experienced hiccup continually for 5 days previous to treatment and was becoming rapidly exhausted. At noon, quinidine sulphate, administered orally in dosages of 10 grains every hour for 3 doses, was vomited. No inhibition of the singultus occurred. At 6:30 P.M., 9 grains of quinidine were administered intramuscularly. The hiccup stopped 2 hours after the 1st dose was given. Two similar doses at intervals of 1 hour were administered and the patient remained free from hiccup until 9 o'clock the next morning at which time the singultus recurred. The hiccup again ceased in 1 hour after the intramuscular administration of 10 grains of quinidine sulphate, and the patient remained

free of singultus for 24 hours. On the 3d day the hiccup recurred. Three successive doses of quinidine, 9 grains intramuscularly, were given. The hiccup stopped after a short time and did not recur for 24 hours. On the 5th night another attack of hiccup ceased after the administration of 9 grains of quinidine intramuscularly. The patient remained free from hiccup, except for 2 short episodes which were not treated, until the 8th day. At this time, the singultus recurred and since the hiccup became continuous and exhausting, he was given quinidine, 9 grains intramuscularly, for 2 weeks at intervals of 1 hour.. The hiccup ceased a short time after the 1st injection. On the 9th day hiccup was again encountered. He received 9 grains of quinidine intramuscularly, at 1:30 P.M. and the singultus ceased at 1:45 P.M. He received another 9 grains of quinidine intramuscularly, at 2:30 P.M. On the 10th day the singultus recurred twice. Following the intramuscular administration of 9 grains of quinidine, the hiccup ceased.

The patient is still in the hospital receiving treatment for his original tuberculous condition, and has not had an episode of hiccup during the remainder of the period of observation (10 days).

COMMENT. In this patient, who had been hiccuping continually for 5 days, quinidine was of definite value in stopping the hiccup. Repeated administration of the drug resulted in cessation of the attack, as a result of which the patient remained free of hiccup for 12 to 24 hours at a time.

CASE 7. D. C., a negro, 62 years of age, was followed in the medical clinic with a diagnosis of singultus apparently of psychogenic origin. He presented a history of episodes of hiccup intermittently for 3 years. Examination showed no abnormalities except a blood pressure at 165/116, and probable slight enlargement of the left ventricle. Treatment was begun at a time when the patient had been hiccuping for 14 hours continuously. Quinidine sulphate, 9 grains, was administered intramuscularly at 10:15 A.M. This was followed by 10 grains orally at 11:15 A.M. A decrease in hiccup was noticed at 1:15 P.M. Ten grains of quinidine were again administered at 1:45 P.M. In about 2 hours the patient's hiccup stopped for a period of 1 hour and 15 minutes. He was then given a maintenance dose of quinidine, 5 grains every 3 hours, throughout the night. Upon returning to the hospital 18 hours later, the patient stated that he had taken the medication as prescribed with no relief from the singultus. He was given 9 grains of quinidine intramuscularly and the hiccup stopped 12 hours later. He had taken a short nap, and it was during this time that the hiccups were relieved. The hiccup recurred 22 hours later. The patient has not returned to the clinic for further study.

COMMENT. It is very difficult to evaluate the results obtained in this patient because he was not under observation during the time in which he was taking the maintenance doses of quinidine. It will be noted that in this case small doses were used and we are not certain that he followed the routine of the prescribed medication.

CASE 8. J. J., a negro, 57 years of age, was admitted to the hospital on October 13, 1947, with a provisional diagnosis of vomiting due to intermittent pyloric obstruction. His blood analyses on admission were typical of a severe alkalosis. The blood sugar was 116 mg. per 100 cc. blood urea nitrogen 78, total blood chloride 337 mg., carbon dioxide combining power 104 volumes per cent. He gave a history which was very incomplete. The following points are significant: He had experienced some epigastric distress for which he had taken fairly large amounts of sodium bicarbonate. He had had no bowel movements for an undetermined period previous to admission. He had been hiccuping continually for 52 hours previous to the institution of treatment and was becoming rapidly exhausted. On October 15, 1947, he was given quinidine sulphate intramuscularly in a dosage of 9 grains every hour for 3 doses. His hiccup stopped 40 minutes after the 1st injection. The relief from hiccup was followed by a rapid improvement in the patient's condition. The patient has had no recurrence of his hiccup for the 8 days he was observed. During this period the abnormal chemical findings returned to normal.

CASE 9. J. S., a negro, 66 years of age, was admitted to the hospital on October 14, 1947, with a diagnosis of hypertensive cardiovascular disease and a recent cerebrovascular accident. He had singultus constantly for 36 hours previous to medication. Quinidine sul-

phate was given intramuscularly in the dosage of 10 grains every hour for 3 injections. The hiccup was noted to have slowed in frequency 30 minutes after the first injection and stopped completely 2 hours after the initial medication, but recurred later that night. Because of the restlessness and extreme illness of the patient, it was considered inadvisable to give more quinidine. He was given 72 grains of sodium amytal intravenously. His hiccup continued, and the next morning he was again given 10 grains of quinidine sulphate intramuscularly every hour for 3 doses. His hiccup ceased 1 hour after the initial injection and remained absent for 62 hours. No further treatment with quinidine was given this patient. The patient died 2 days later following another cerebrovascular episode.

Discussion. Although not discussed in detail in the case reports, (except for Case 1), the usual well-known methods of treatment of hiccup were tried in most of these patients with little or no success. Our experiences in the above group of patients suggest that quinidine has an apparently beneficial effect in controlling attacks of hiccup. The possible theoretical basis for its action is discussed below. In our patients the drug was given by mouth, intramuscularly, and in 1 patient intravenously. While it is felt that administration by mouth is effectual, its action is apparently more dependable when given by the parenteral route. By the intramuscular route the absorption is certain, uniform, and relatively safe. It is felt that a more effective response will be obtained by the use of high doses given over a relatively short period of time rather than small doses given over a prolonged period. Such a procedure has recently been shown to be a more satisfactory one in the treatment of many cases of ventricular tachycardia. Delevett and Poindexter[5] have shown that when a single dose of 15 grains of this drug is given by mouth the concentration reaches its maximum in a period of from 2 to 4 hours, and that it required a certain level in the blood, namely about 1 mg. per liter, to stop an attack of nodal tachycardia. It is quite likely that a similar situation may exist in respect to hiccup. That this drug may not work equally well in all cases will depend upon the underlying cause of the increased irritability and its degree. We are as yet not certain as to the dose of the drug and frequency of administration which may be necessary to stop a paroxysm. At present it is suggested that an initial dose of 10 grains, preferably given by the intramuscular route, be repeated hourly for 3 to 4 doses. If the paroxysm stops, the patient may be put on a maintenance dose of 5 grains orally every 2 to 3 hours. If the paroxysm recurs, the initial high doses should be repeated. The use of cinchona derivatives in man by mouth and by vein has already been extensive enough to demonstrate their relative safety.

The use of quinidine is not recommended in all patients. It is suggested for those cases of persistent hiccup where the usual procedures are ineffective and where the continuance of the paroxysms results in exhaustion of the patient.

Probable Mechanism of Action. That the cinchona alkaloids have a pronounced effect on striated muscle was recognized by Santesson[15] (1892), Secher[16] (1915), Fürth and Schwartz[6] (1909), and Harvey[9] (1939). Brody and Sollman[2] (1923) showed that quinidine lengthens the refractory period of skeletal muscle. The results obtained by these authors in experiments with quinidine on striated muscle were quite parallel to the clinical results with quinidine in auricular fibrillation, as conceived by Lewis and others. These authors state that "In both cases the prolongation of the refractory period makes the muscle independent of a rapid rate of stimulation that ordinarily produces more or less complete tetanus and enables it to adopt the slower rhythm and more extensive excursions that are so much more efficient for working a pumping mechanism." Harvey[9] (1939) showed that quinine

decreases the ability of the muscle to respond to and hold a tetanus. This is due to an effect directly on the muscle which increases the refractory period. The excitability of the motor end plate is lowered, so that the response to nerve stimulation is reduced. This is best seen in a partially curarized muscle. When quinine is injected under these conditions, the curarization becomes complete. This action is also in part responsible for the abolition by quinine of the quick response of the muscle to injected acetylcholine. That quinine may have a direct effect on nerve tissue is suggested by Stravaky[17] who found quinine acts directly as a paralyzing drug on the secretory fibers of the auriculo-temporal nerves.

The normal potentiation of the twitches caused by physostigmine due to repetitive response to a single nerve volley, is prevented by the previous administration of quinine or is counteracted promptly when the drug is injected during a period of potentiation.[12] Weiss found that the fibrillary twitchings produced in the cat by prostigmine were abolished by the intravenous injection of quinine. The repetitive response to a single stimulus which occurs after veratrine is also removed by quinine. This occurs in both the normal muscle and the muscle of which the motor nerve has previously been cut and allowed to degenerate. Harvey[9] (1940) has shown that the curareform action of quinine is greatly increased by the introduction of the quaternary ammonium ion in the quinoline ring as observed by the action of quinine methochloride. The main features of the action of quinine methochloride on the mammalian nerve muscle preparation resembles curarine, blocking neuromuscular transmission and leaving the response of the muscle to direct stimulation unimpaired. Like curarine, it causes a depression of the response of the motor end plate and the ganglion cell to nerve impulses and to acetylcholine, but does not interfere with the normal liberation of acetylcholine from the preganglionic nerve endings. This drug has been used successfully in the prevention of fractures in the course of convulsive therapy with metrazol.[1] Wolf[20] (1936) showed the value of quinine in the treatment of myotonia congenita. The chief clinical manifestation in this condition is a contraction in skeletal muscle after the end of a voluntary stimulation. This state is symptomatically relieved by quinine but is made worse by prostigmine. Quinine increases the muscular weakness of patients with myasthenia gravis, thus manifesting an opposite effect to that of prostigmine in these 2 conditions.[8,9,11] The cinchona drugs have also proven of value in the treatment of night cramps of the lower extremities.[7,13] This condition appears to be due to a lasting tetanic contraction of a muscle group due to reflex bombardment of the myoneural junction by a stream of impulses from some neighboring source of irritation. The effectiveness of quinine here is due in part to its action directly on muscle tissue, but more important is its effect in interrupting the reflex arc by blocking myoneural pulse-transmission. To quote Gootnick,[7] "Quinine acts in relieving night cramps much as does digitalis in depressing the bundle of His in auricular fibrillation by cutting down the number of impulses that can get through to stimulate the muscle to contraction."

If attacks of hiccup are the result of spasmodic contractions of the diaphragm and other muscles of respiration, the impulses for which are transmitted through nerve tissue, it is our feeling that quinidine could stop a paroxysm of hiccup in 2 ways: (1) by a direct effect of the drug on the diaphragm as well as on the muscles of respiration; and (2) by blocking the nerve impulses at the myoneural junction. There is some suggestive evidence that this drug may have a direct effect on nerve tissue which may block impulses through the vagus and other nerves.

Summary. 1. Experience with the use of quinidine in the treatment of 9 cases of hiccup is discussed. Quinidine was appar-

ently effectual in stopping the paroxysms in 6 cases, was partially successful in 2 and failed in 1 case.

2. In patients with intractable hiccup the use of this drug may be efficacious in stopping the seizures when other methods have failed.

3. The probable mechanism of the action of quinidine in the treatment of hiccup is discussed.

Addendum: Since this paper was submitted for publication, our experience with subsequent cases of hiccup has been somewhat similar to that reported above. One point of interest might be added: in those patients where hiccup followed abdominal operations and subsequent fluid loss by vomiting or other means, electrolyte imbalance, notably hypocalcemia and hypopotassemia, was apparently a factor which tended to induce or help maintain the attack of hiccup. In addition to the administration of quinidine, the correction of this electrolyte imbalance was an important factor in stopping the hiccup attacks.

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SULFATE AND PHOSPHATE EXCRETION IN URINE OF PATIENTS ON RICE DIET*

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THE course of renal and hypertensive vascular diseases has been modified by the use of a diet consisting of rice, fruit, and sugar.[5,6,7,8] Ninety-five per cent of the caloric intake is furnished by carbohydrate; in 2000 calories there are about 20 gm. of protein and not more than 5 gm. of fat, 0.2 gm. of chloride, and 0.15 gm. of sodium. On this regime the nitrogen equilibrium is maintained, and the patient can be made to gain weight if the caloric intake is raised.

Quantitative data on all aspects of metabolism are needed to determine the factors responsible for the favorable effect of the rice diet on the course of hypertensive and renal diseases. This paper summarizes the changes in urinary phosphate and sulfate excretion which occur on the rice diet.

Procedure. The sulfate and phosphate were measured in each of 3 successive 24 hour urine collections. The sulfates were determined by the benzidine method of Rosenheimer and Drummond as modified by Hoffman and Osgood.[4] The inorganic phosphate P was determined with a photo-electric colorimeter according to the phosphomolybdate method of Fiske and SubbaRow.[2]

The studies were carried out on patients with hypertensive vascular disease without evidence of renal failure. The diet of many of the patients had been restricted before the rice diet was started. The daily urinary excretion of total sulfate and of inorganic sulfate was determined in 14 patients (10 men and 4 women) who had followed the rice diet for periods of 30 to 46 days (average 36 days). The urinary inorganic phosphate was measured in 17 patients (13 men and 4 women) who had followed the diet for 14 to 59 days (average 34 days).

The results are summarized in Table 1.

The inorganic sulfate excretion in all 14 patients showed a decrease ranging from 68 to 92% (average 82%). The ethereal sulfate excretion increased in 2 patients and fell in 12. For the 14 patients the average decrease was 56%. The total sulfate excretion in all 14 patients showed a decrease ranging from 58 to 91% (average 79%). The ratios of inorganic sulfate to total sulfate ranged from 0.56 to 0.90, average, 0.77, before the diet, and from 0.41 to 0.81, average 0.65, after the diet.

The inorganic phosphate excretion in all 17 patients fell from 40 to 75%, with an average fall of 62%.

In Table 2, the lowest amounts of

TABLE 1.—EFFECT OF RICE DIET ON SULFATE AND INORGANIC PHOSPHATE EXCRETION IN URINE OF PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

	Range		Average	
	Before	After Rice Diet	Before	After Rice Diet
Total Sulfate (mg S in 24 hrs.)	761–471	254–58	592	126
Inorganic Sulfate (mg S in 24 hrs.)	547–362	165–40	452	81
Ethereal Sulfate (mg S in 24 hrs.)	328–52	115–15	140	45
Inorganic Phosphate (mg P in 24 hrs.)	1055–501	435–170	761	289

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sulfate and phosphate in a single 24 hour urine collection in this group of patients are recorded and compared with the amounts excreted on an egg-milk diet, a starch-cream diet and in fasting.

Discussion. The data are of value for two reasons. First, they demonstrate that the kidney is called upon to excrete much less phosphate and sulfate when a patient is on the rice diet than when he is on a regular diet or while fasting. What this means in terms of renal work is not known. Observations are needed on patients with hypertensive disease on a rice diet with added phosphate and sulfate. Secondly, these data serve as a rough check on the data previously reported on nitrogen equilibrium.[6] The patients had a daily protein intake of 20-25 gm. But they could not have been breaking down appreciable amounts of body protein because of the low excretion of nitrogen, phosphates, and sulfates as compared to that of fasting individuals.

Summary. The average amount of inorganic sulfate excreted in the urine of 14 patients on the rice diet was about 90% lower than that of persons on a normal diet; the average amount of ethereal sulfate was about 45% lower, that of total sulfate was about 85% lower. The average amount of inorganic phosphate was about 70% lower than that of persons on a normal diet.

TABLE 2.—MAXIMAL-MINIMAL URINARY SULFATE AND PHOSPHATE EXCRETION ON EGG-MILK DIET, STARCH-CREAM DIET, FAST AND RICE DIET

	Egg-Milk Diet* (120 gm. of protein)	Starch-Cream Diet* (6 gm. of protein)	Fasting§ (10th day)	Rice Diet (20-25 gm. of protein)
	Highest Values	Lowest Values		Lowest Values
Total Sulfate (mg S in 24 hrs.)	1315†	194†	579†	50
Inorganic Sulfate (mg S in 24 hrs.)	1252	168		25
Ethereal Sulfate (mg S in 24 hrs.)	76	24		2
Inorganic Phosphate (mg P in 24 hrs.)	1613‡	276‡	709‡	117

* According to Folin[3]
§ According to Benedict[1]
† Calculated as 90% of Total Sulfur.
‡ Calculated as 90% of Total Phosphorus

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BRUCELLOSIS AND MULTIPLE SCLEROSIS

CUTANEOUS REACTIONS TO BRUCELLA ANTIGENS

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BECAUSE of the multiplicity of its manifestation, brucellosis has often been compared to syphilis. Innumerable case reports attest the ability of acute brucellosis to produce focal disease of all sorts. In the central nervous system it may cause meningitis, encephalitis, and encephalomyelitis. It is also well known that chronic Brucella infection produces lesions in the eye.

We have reviewed 560 cases of chronic brucellosis to determine the frequency of neurologic symptoms. Definite sensory and motor changes or disturbances of the 2nd, 6th, or 8th nerves were found in 28 patients; in 2 additional patients the fully developed picture of multiple sclerosis was present. This suggests the possibility that multiple sclerosis might be a central nervous system manifestation of chronic brucellosis.

In order to investigate this hypothesis 118 consecutive cases of multiple sclerosis have been studied. The diagnosis was made in each case by a member of the neurosurgical or neuropsychiatric departments of the Cleveland Clinic.

Methods. Three methods of Brucella skin testing were employed. An unaltered, heat-killed, suspension of suis and abortus strains of Brucella combined (6 billion per cc.) was used as the standard test on all patients throughout the study. Each intradermal injection consisted of 0.04 cc. Brucellergen (0.1 cc.) and Brucella antiserum (0.04 cc.) the latter according to the technique of Foshay[4] were used as confirmatory tests in about half the cases of multiple sclerosis.

Skin tests were used on 2 control groups. Group 1 consisted of 56 rural residents of middle ages having a variety of clinical disorders. Group 2 was comprised of patients with neurologic conditions other than multiple sclerosis or encephalomyelitis.

Definite standards of interpretation were established. The standard vaccine type or bacterin test was read according to Harris,[5] description of this method. The evolution of this reaction commonly requires 48 to 72 hours to reach its maximum, but nonspecific reactions of erythema without induration may be seen in the first 24-hour period. In those in whom the response is feeble, the persistence of induration and discoloration for a week or more supports the positive interpretation of the reaction. Hence, a positive reaction is recorded when there is a visible and palpable infiltration of the dermis accompanied by a surrounding erythema.

Brucellergen produces a more delicate and rapid reaction than the bacterin method. A positive reaction is recorded when there is edema and erythema between 24 and 48 hours. A positive antiserum reaction consists of a central wheal with a surrounding flare averaging 4 to 5 cm. in diameter appearing within 10 minutes of the injection. The interpretation of antiserum reactions is facilitated by the use of a control injection of nonimmune or specially filtered serum.

Results. The results of the 3 types

of cutaneous tests in the multiple sclerosis group are given in Table 1.

TABLE 1. RESULTS OF DIAGNOSTIC TESTS FOR BRUCELLOSIS IN 118 CASES OF MULTIPLE SCLEROSIS

Test	Total cases	Negative	Positive	Per cent positive
Killed Brucella organisms	118	3	115	97
Brucellergen	55	2	53	96
Polyvalent anti-brucella serum	55	0	55	100
Antiabortus serum	55	0	55	100
Filtered serum	44	38	6	14

The results of the bacterin test in the control groups are given in Table 2.

TABLE 2. RESULTS OF BACTERIN TESTS FOR BRUCELLOSIS IN 98 CONTROL CASES

	Total cases	Negative	Positive	Per cent positive
Group 1	56	44	12	21
Group 2	42	29	13	31

Three patients with multiple sclerosis are listed as having negative bacterin tests. In 1 of these patients it was not possible to observe the reaction at the proper time nor to secure a satisfactory description. It was therefore recorded as negative. This patient did have a positive reaction to each antiserum test. The other 2 patients with negative bacterin reactions were not tested with Brucellergen or antiserum tests. The 2 patients who had negative Brucellergen tests had definite positive reactions to bacterin and to antisera as well. Of the positive reactions to bacterin 10 were classed as weakly positive. In these erythema was less than 2 cm. in diameter, but in all cases induration and discoloration were present for at least a week. Seventy-nine of the positive bacterin reactions were graded as moderately positive with erythema of 2 to 4 cm. in diameter, and 26 cases exhibited more extensive erythema and were termed strongly positive. Actual tissue necrosis occurred in 6 of these. Approximately the same proportion of weak, moderate, and strongly positive reactions were seen among the patients in the control groups.

To be certain that the positive reactions observed in multiple sclerosis were not the result of an abnormal degree of cutaneous reactivity, the latest patients in the series were also tested with 0.1 cc. each of old tuberculin (1:10,000), histoplasmin (1:1000), and coccidioidin (1:1000). The results of these tests are given in Table 3.

TABLE 3. RESULTS OF TUBERCULIN, HISTOPLASMIN AND COCCIDIOIDIN TESTS IN 10 CASES OF MULTIPLE SCLEROSIS

	Patients	Positive	Negative
Old Tuberculin	41	15	26
Histoplasmin	34	5	29
Coccidioidin	34	0	34

A foreign body effect on the part of the whole organism appears not to be involved. This factor was investigated by skin testing 10 patients with a vaccine of *H. influenzae* and 19 with a vaccine prepared from a streptococcus isolated from sour cream. Neither of these preparations produced any persisting induration or erythema.

The possibility that the skin reactions were due to other types of infection is more difficult to evaluate. Cross agglutination reactions definitely occur between brucellosis, tularemia, cholera, Flexner type dysentery, and *B. proteus* infections. However, there was nothing to suggest the presence of any of these infections, other than brucellosis, in any of the patients studied.

The cutaneous antiserum reaction of Foshay,[4] even more than Brucellergen, speaks for the specificity of the Brucella

reactions. Foshay has shown that the antiserum reaction was specific for 19 different strains of streptococci. He found that the test involved a reaction between an antibody to the specific polysaccharide of an organism and the polysaccharide itself which is deposited in the tissues of the infected person. This antibody could be removed by filtration through Fuller's earth without lowering the titer of agglutinins. The control serum used in this study was prepared in this manner. Foshay has cautioned against the possibility of false positive reactions from commercial preparations because they may contain antibodies to polysaccharides of incidental organisms. Twenty-five Brucella negative individuals have been tested with the polyvalent antiserum and 3 reacted positively.

Forty Brucella positive patients who did not have multiple sclerosis were tested with the polyvalent antiserum and were found positive in all instances, although in 2 the reaction was delayed 24 hours. It is felt that the high frequency of positive reactions to Brucella antiserum in cases of multiple sclerosis is further evidence of the possible existence of brucellosis in these individuals. The fact that all cases tested reacted to antiabortus serum as well as the polyvalent antiserum may be of some significance. Foshay reported a limited experience with the several types of Brucella antiserum but indicated that the cutaneous reactions were specific for melitensis, suis, or abortus strains. The writers have encountered only 1 Brucella positive patient who reacted to polyvalent antiserum but failed to react to antiabortus serum.

Agglutination reactions were done in 23 cases of multiple sclerosis. The reaction was negative in 18 and positive in 5 in titers of 1:20, 1:20, 1:40, 1:160, and 1:320, respectively. The last 2 titers must be discounted because they were taken 4 to 5 weeks following the skin test. Although one would expect to find low titers in chronic infections and negative reactions in those in whom the infection is in an inactive stage, these figures are still far from impressive. Eisele, McCullough and Beal[3] have pointed out some of the vagaries of the agglutination reaction.

As a further check on the agglutinations Eisele generously consented to test specimens of our patients' sera in the University of Chicago laboratory. The results in his laboratory and those in the Cleveland Clinic are given in Table 4.

TABLE 4. COMPARISON OF AGGLUTINATION TEST RESULTS IN 2 LABORATORIES

Patient	Cleveland	Chicago (Dr. Eisele)
1	negative	1–80
2	1–20	1–80
3	negative	negative
4	1–360	1–1280 and partial 1–2560
5	negative	1–40
6	1–160	1–320
7	negative	1–40
8	negative	negative
9	negative	1–20
10	negative	negative
11	negative	negative
12	negative	negative

All of these patients had positive skin tests and all but patients 2 and 11 had multiple sclerosis. The differences are striking and, like the laboratory discrepancies noted by Eisele *et al.*, are probably due to differences in sensitivity and selectivity of the antigens. Cases 4 and 6 were those taken several weeks after the skin test. The extremely high titer in case 4 could not be wholly the result of the previous skin test, but that in case 6 might be. Consequently, if the latter case be excluded, the agglutination test was positive in 5 out of 9 cases of multiple sclerosis. All multiple sclerosis patients with positive reactions had evidence of active disease; those in whom the ag-

glutinations were negative showed few if any new neurologic signs.

Discussion. The peculiar geographic distribution of multiple sclerosis is one of its most distinctive features. In the United States the areas of greatest frequency are in the Pacific Northwest and in the Great Lakes basin. These regions are characterized by excessive rainfall, little sunshine, and high milk production. Brucellosis of the abortus type is also prevalent in these areas.

The question naturally arises as to whether the concept of brucellosis as an etiologic agent in multiple sclerosis is compatible with recent fundamental work in the pathogenesis of the latter disorder. An excellent review of this subject has been published recently by Andren.[1] He contends that neither the possibility of local allergy nor the theory of virus etiology necessarily precludes the possibility of vasoconstriction or vascular occlusion as the basic mechanism in multiple sclerosis. The same statement could be applied to brucellosis. Perivascular infiltration, and small vessel thromboses have been noted as basic components of the granulomatous lesions known to be produced by that disease. The plaque-like lesions seen in cases of Brucella chorioretinitis are certainly comparable to the plaques of multiple sclerosis and both chorioretinitis and iritis have been seen in a few of the patients of this study.

A case of multiple sclerosis[2] occurring during the course of a remittent Brucella infection has been reported in the French literature. Roger *et al.*[8] reported a case of neuromyelitis optica, (essentially an acute and rapidly fatal form of multiple sclerosis), with a Brucella agglutination titer of 1:800 in the spinal fluid. A similar case without fatal termination was reported by McCullagh and Clodfelter.[6] Roger[7] has also recorded 10 cases of brucellosis in which there were transient sensory and motor disturbances which he believed to be the result of cerebral vasospasm occurring during both the early and late course of the disease. A mild cyto-albuminous reaction in the spinal fluid was found in 9 of the cases and a positive culture was obtained in one.

The investigations of Teague[9] have been cited as evidence against the infectious origin of multiple sclerosis. He reported failure to isolate spirochetes from the blood and spinal fluid of cases of multiple sclerosis as had been previously reported. He also recorded that some of the rabbits inoculated with blood or spinal fluid died of wasting infections with an unidentified small, gram negative bacillus in the blood stream. We have inoculated both rabbits and guinea pigs with blood and spinal fluid from 5 cases of multiple sclerosis all exhibiting signs of recent activity. The only definite result to date is the acquisition of a deep regard for the difficulties encountered in this sort of investigation. A number of animals have died of a granulomatous disease, but cultures have been either sterile or contaminated.

Summary. 1. A high degree of cutaneous reactivity to Brucella antigens has been found in a group of patients with multiple sclerosis.

2. The known pathologic features and geographic distribution of multiple sclerosis and brucellosis are not incompatible with some relationship. The possibility of a connection between these two diseases warrants further investigation.

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ERRATUM

In the article on an Epidemic of Tularemia, Figs. 4 and 5 on pages 421 and 422 of the October issue, should be reversed; *i.e.*, the illustration marked Fig. 4 should appear above Fig. 5 on next page, and vice versa.

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PROGRESS
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GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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ENDOMETRIOSIS

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THE pathological entity classified under the name of endometriosis has attracted widespread attention since it was first described*. It is a condition in which endometrium is situated in a position in the body other than in its normal confines in the uterine cavity. Two general pathological types exist. The first, known as adenomyosis, or internal endometriosis, exists in the muscular wall of the uterus itself, and the second, known generally as external endometriosis, consists of the seeding and development of endometrial implants in locations outside of the uterine wall itself. The latter type may be present in any one of a great variety of positions. These endometrial implants respond physiologically to cyclic hormonal stimuli from the gonads, and have been demonstrated to have the same structural changes as normally situated endometrium at the various phases of the ovarian cycle.

Etiology. The true cause of endometriosis is still unknown, but many theories have been advanced in an effort to explain the occurrence of this pathological condition. Only a few have withstood the tests of time and the laboratory. Ranney[66] has classified these theories into two main groups: (1) theories concerning histogenesis, and (2) that concerning possible stimulating influences. Those concerning histogenesis are as follows:

1. *Ectopic endometrium transported from the uterus to the pathological site.* This theory was introduced by Sampson[71] in the early 1920's. It was based on his own clinical observations and studies in pathology. In essence, Sampson's theory postulated that bits of uterine and tubal epithelium were discharged through the fimbriated ends of the tubes by retrograde flow during menstruation, and that they implanted usually on the ovaries, but occasionally on the pelvic peritoneum, or on the serosa of nearby structures, especially in convenient peritoneal pockets. Sampson had observed that endometriosis

* See Block's[6] earlier review (1940) in this section.

was seldom discovered in women under 30 years of age, and that bilateral tubal patency was present in 97% of the patients he had studied. He noted, too, that endometrial hematomas usually developed on the lateral and inferior surfaces of the ovaries, which are the parts most likely to be contaminated by material regurgitated from the tubes. This theory served to awaken a tremendous interest amongst workers in gynecologic and related fields, and soon the theory was subjected to many clinical and laboratory tests. Endometrial tissue has been artificially transplanted into the liver, spleen, abdominal wall, and anterior chamber of the eye in smaller animals. Typical adenomas of various sizes were formed as a result of this autotransplantation, and these were lined with ciliated columnar epithelium, and contained fluid under pressure. Novak and TeLinde,[59] however, claimed that menstruating endometrium discharged from the uterus is necrotic, and contains chiefly autolyzed constituents, with few, if any, formed elements. It has subsequently been shown that endometrium obtained during menstruation is scarcely viable and hardly able to grow in a manner comparable with intermenstrual endometrial particles.

2. *Mechanical transplantation theory.* There is no doubt that endometrial tissue can be transplanted during surgical procedures. Numerous cases have been reported in which endometriosis has been found in laparotomy scars following pelvic surgery.[7,58,68,83] A case of endometriosis[75] in an episiotomy scar following a normal spontaneous delivery has recently been reported. Numerous writers have reported the transplantation of endometrial tissue to pelvic structures following curettage of the uterus. Endometrial tissue has been successfully transplanted into the pleural and peritoneal cavities in experimental animals. The successful implants usually assume a cystic nature, and respond to the normal ovarian stimulation.

3. *Metastasis theory.* The presence of endometrial tissue beneath the apparently normal peritoneum is not explainable except on the basis of spread through the lymphatic channels draining the uterus. The evidence for lymphatic metastasis is incomplete, and it is likely that further studies on this mode of transmission will be carried on in the laboratory. The other route of metastasis suggested is *via* the blood stream, particularly the venous channels. The evidence in favor of this lies in the reported occurrence of instances of endometriosis in the extremities. The evidence supporting this theory is far from complete, however, and this concept would at best explain only a very small number of cases.

The theory evolving from the concept of ectopic endometrium developed in situ from local cells is as follows:

1. *Celomic metaplasia theory.* The Muellerian duct is derived from the embryonic celomic epithelium and mesenchyme, and forms most of the female genital tract including the endometrium. Other adult derivatives of the embryonic celomic cells may retain the potentiality of forming tissue which is indistinguishable from endometrial tissue. Gruenwald[29] implies simply that the cells which are descendants of the celomic epithelium and which may retain the potentiality of endometrium formation, are present in large numbers in the upper genital organs and pelvic peritoneum. These are present also, to a far lesser extent in the extremities, the upper two-thirds of the vagina, the pleura, the general peritoneal cavity, the umbilicus, and other locations in which endometriosis has been discovered, including the inguinal canal, the serosal surface of the bladder and ureters. The celomic metaplasia theory permits a physiological

explanation, based on embryological and pathological observations, for endometriosis occurring spontaneously in any part of the body, provided, of course, that the basic concept of celomic cell rests can be proven. Conclusive proof of the validity of this theory is at present lacking, and may never be available. As would be expected in a disease whose etiology is so obscure, many other attempts have been made to explain the cause, but none has withstood laboratory experimentation or clinical findings. Perhaps a combination of the theory of Sampson, plus the mechanical transplantation theory and the theory of lymphatic metastasis will serve best to explain the etiology insofar as our present knowledge permits.

Incidence. Endometriosis is a disease of women in the childbearing age. Its greatest incidence occurs in the last part of the third decade of life and early part of the fourth decade, but it has been reported as occurring at earlier ages,[20] during the years of waning ovarian stimulation, and in postmenopausal ages.[25] It is probable in many instances that the disease process is initiated at an early age, and is not suspected or discovered until increasing severity of symptoms calls for medical investigation or laparotomy. Fallon[21] and Holmes[36] have both presented evidence suggesting that increasing dysmenorrhea and pelvic pain occurring in the second decade may repre the beginning of endometriosis.

It is impossible to estimate with any accuracy the incidence of endometriosis in the population at large. A great variability is noted in the methods of reporting it. Haydon[30] reports an incidence of 9.84%. Holmes[36] reports an operative incidence of 26%. Sampson has reported endometriosis in 21.6% to 29.5% of his series of gynecologic laparotomies. Meigs[53] reports an incidence of 28% in his private practice as opposed to one of 5.8% in the Massachusetts Hospital group. Hunter, Smith and Reiner[31] report an incidence of adenomyosis of 27.8% in a series of 1856 hysterectomies performed for all causes over a 15 year period. Yin[84] states that endometriosis and adenomyosis are commonly found in Chinese women. Lock and Myers[45] report an incidence of 28% of proven cases in their series. Endometriosis has been recognized more frequently in recent years. It is not certain whether this has been an absolute or relative increase, since many more physicians than ever before are seeking this condition because of its recognized serious implications. Meigs[52] has attributed the increase to several factors. One of these is the modern economic trend favoring delayed marriage, and delayed and infrequent childbearing. Meigs is of the opinion that menstruation is not supposed to occur monthly for years without interruption, resulting in many menstrual cycles without union of the sperm and ovum. Stimulation by the varied hormonal reactions of menstruation of the celomic cells might cause them to grow and produce Muellerian growth. This view is supported by his statistics showing an incidence of 28% in his private practice as opposed to one of 5.8% at the Massachusetts General Hospital. He advocates early marriage, and early and frequent childbearing to offset the increasing incidence.

Pathology. The pathological features of endometriosis consist of aberrant masses of endometrial tissue in a variety of locations. The ectopic tissue found in these locations has all the macroscopic and microscopic features of endometrium normally situated. There is a tendency to glandular and cystic formations. These respond to the various endocrine influences exerted on the endometrium during the menstrual cycle. Since most of these cysts have no outlet, there is usually pain as-

sociated with the onset of the menses. As these masses of endometrium continue their life cycles, a great deal of fibrosis and scarring occurs in the organs concerned, and dense adhesions develop between the serous coats of the organs. These adhesions are usually deep seated and their separation is very difficult because of the involvement of the seromuscular layers. Mucosal involvement of the bowel does not as a rule occur, but has been reported.[12] When the full thickness of the viscus is invaded, bleeding into the lumen may result. Thickening of the bowel wall and proliferation of the smooth muscle may encroach on the lumen of the bowel, and produce a partial or complete obstruction. It is frequently very difficult to differentiate grossly this type of endometriosis of the bowel from carcinoma.

The organs most frequently involved in this disease process are, in the order of frequency, the ovaries, pelvic peritoneum (posterior cul-de-sac with involvement of the uterosacral ligaments), external surface of the uterus, rectovaginal septum, bladder, Fallopian tubes, and sigmoid colon.[30,39,53,65,80] More rarely, the round ligaments, appendix, umbilicus, and other peritoneal organs are involved. In rare instances, endometriosis of the extremities[73] has been reported. Endometriosis of the lungs has been produced experimentally in laboratory animals.[33,34]

The lesions in the ovaries vary in size from that of a pinhead to that of a grapefruit. They vary in color from dusky red to brownish black. The cysts are usually chocolate colored due to discoloration of the thin cyst wall by the contents of the cyst. The thicker walled cysts, however, are somewhat whitish and dull. These cysts characteristically perforate when the intraluminal pressure becomes too great for the cyst wall to withstand, and the organization of the blood which escapes from the cyst seals the defect, and bloody fluid again accumulates within the cyst cavity. This organization process results in peri-ovarian adhesions. Other organs in the pelvis are also involved in these adhesions. The pelvic peritoneum may become hyperplastic and present a picture of chronic inflammation. Endometrial implants on the anterior surface of the uterus may produce typical peritoneal adhesions to, and invasion of, the bladder. This may extend through the entire thickness of the wall of the bladder and give rise to hematuria and other urinary symptoms. The characteristic puckering of the peritoneal covering of the bladder is apparent at operation.

More infrequently, endometriosis occurs in regions of the body that are more or less remote from the genital organs. Less than 100 cases of endometriosis of the umbilicus have been reported in the world literature. Endometriosis of the intraperitoneal portion of the round ligament occurs rather frequently, but only a few cases of the disease have been reported as occurring in the inguinal portion of the round ligament. When this occurs, it may be quite difficult to differentiate it from hernia.[16,24] Endometriosis of laparotomy scars are noted by many authors. The majority of these occur following operations on the uterus or Fallopian tubes. Wood, Diebert and Kain[81] reported a case of endometriosis which was located in the ileum, 3 inches from the ileocecal junction. The lesion in this case was hard, and consisted of a constricting band of fibrous tissue. Schlicke[73] has reported a case of endometriosis in a 35 year old Filipino which occurred on the posterior aspect of the left thigh. Clinical endometriosis of the lungs has not yet been reported, but Hobbs and Bortnick[33] think that many cases may be mistakenly diagnosed as tuberculosis, cancer or benign lung tumors, and they are of the

opinion that, if sought, many cases of endometriosis might be discovered. Primary endometriosis of the cervix uteri is very rare.[35] To date, there have been only a few cases of perineal endometriosis following episiotomy, and only one in a spontaneous delivery.[74] Endometriosis is not frequently found in association with malignancy of the generative organs.

Symptoms. It is generally agreed that the most constant symptom of this disease is dysmenorrhea. This is of the acquired type, and usually progressive. Counseller[14] states that vesical and, or, rectal pain superimposed on an acquired dysmenorrhea is almost always diagnostic. Diffuse pelvic soreness, brought about or aggravated by walking or jarring of the pelvis in any way is also suggestive. Dyspareunia is frequently a presenting symptom. Most of the patients are found to be infertile, despite the fact that patent tubes are found in a large percentage of cases. When endometriosis is found to be the cause or an associated factor in a sterility problem, the solution is frequently very difficult, for a cure of the endometriosis too often requires a radical procedure on the reproductive organs. Even in those cases in which conservative measures are carried out, the results as far as fertility is concerned are not often satisfactory.

Jeffcoate[38] has demonstrated that in about 10% of his patients with endometriosis, pyrexia was a significant factor in making the diagnosis. The degree of fever was not high, 101 to 102° F. being the highest recorded, and its occurrence variable, as it is sometimes intermittent throughout the cycle. The hyperpyrexia typically occurs *during* menstruation, and gradually disappears 1 to 2 days after the flow has ceased. Body temperature normally rises premenstrually, and falls with the onset of flow, so that an elevation *during* each period should be regarded with suspicion. Other chains of symptoms may develop with involvement of other organs. The ureters may be constricted and produce symptoms of the associated hydronephrosis or ureteral colic. Intestinal obstruction may develop. Localized bluish swelling of isolated lesions in the extremities or in postoperative scars may develop during the menstrual periods. Bimanual examination of the pelvis is very important in making the diagnosis. One may find a cystic ovarian mass, which is usually very tender. Beading of the uterosacral ligaments is characteristic when present. Generalized tenderness throughout the pelvis may be found, and may necessitate an examination under anesthesia.

A careful case history, taken with a high index of suspicion, is necessary for diagnosis of this disease. A careful log of the menstrual periods of the patient, with special reference to the presence of increasing dysmenorrhea, infertility, and dyspareunia, and pelvic pain on urination and defecation is essential for the diagnosis.

Complications. It is important to recognize that symptoms may arise in organ systems other than the genital tract. The most frequently involved extragenital systems are the urinary and the gastro-intestinal tracts. Glenn and Thornton[26] reported 2 cases of obstructing endometriosis of the ileum in 1940. They were able to find only 4 similar cases in the literature. Wood, Diebert and Kain[81] reported a hard fibrous constricting band only 3 inches from the ileocecal junction which proved to be an endometrioma on microscopic examination. This is the only case of a similar nature reported since Glenn and Thornton's report. Sutler[79] states that the intestinal tract is a highly significant extragenital location for endometriosis. He found involvement of the intestinal tract in 35 patients; the appendix in 25, the ileum

in 1, and the rectosigmoid in 9. Thierstein and Allen[50] differentiate between a deep and superficial type of endometriosis of the bowel, and state that the former is more likely to be the cause of intestinal obstruction. The radiologic picture of intestinal obstruction due to endometriosis is somewhat characteristic. Jenkinson and Brown[39] have reported relatively long filling defects of 4 to 7 inches demonstrable by barium enema, which are sharply demarcated as in carcinoma. Fixation and exquisite tenderness on palpation are found during fluoroscopic examination. The mucous membrane, however, is essentially intact. In carcinoma of the bowel, the mucosa is usually involved, and the constant filling defect is not so tender to palpation. McGuff, Dockerty, Waugh and Randall[51] reported 16 cases of intestinal obstruction due to endometriosis, which represent the total seen at the Mayo Clinic. They stressed the presence of the usual symptoms of endometriosis, plus the presence of a long history of intestinal symptoms which suggest progressive intestinal obstruction with frequent exacerbations at the menses as the most important points in establishing the clinical diagnosis of this disease. Diarrhea and vomiting, frequently found in intestinal obstruction from other causes, are encountered, but the presence of gross blood in the stools is almost never encountered. When it is found at the time of the menstrual period, it is of significance. Sigmoidoscopic examination almost always reveals the presence of an intact mucous membrane. Patton and Patton[62] have emphasized the absence of lymph node changes, which is helpful in making the gross diagnosis at the operating table.

Endometriosis of the *urinary bladder* may occur in any woman of menstrual age. In a series of 46 patients with endometriosis of the bladder collected by Moore, Herring and McCannel,[56] 42 had had either previous pelvic operations, or, at the time of examination had some disease of the reproductive system. Kahle, Vickery and Maltry[41] had previously noted this fact, and the report by O'Conor and Greenhill[61] adds confirmation. Dreyfuss[18] presented a case of so-called "internal endometriosis" of the bladder, in which the endometrial cells were thought to originate from bladder epithelium. No serosal or other implants were found at operation. This is the only report encountered in the literature that makes mention of this type. O'Conor found in 7 of the 58 patients whom he studied that the endometriosis was supposedly confined to the bladder with no other intra-abdominal lesion present. Leventhal and Solomon[44] reported a case of slow constriction of the ureters by an endometrioma of the pelvic peritoneum and rectovaginal septum. In this case, the ureters were displaced medially, and a bilateral hydronephrosis was demonstrated. Urinary complaints are usually cyclic, and consist of bladder fullness, dysuria, frequency and urgency. The severity of these symptoms vary, the intensity being dependent upon the proximity of the lesion to the trigone, and upon the size of the endometrioma. Hematuria occurs only if the mucosa of the bladder is invaded. It was reported in only 13 of Moore's 46 cases, and in less than one-third of O'Conor's series. The lesion is palpable in the base of the bladder in about half of the cases. If the mucosa is involved, the lesion is easily identified by cystoscopic examination. A bluish-black tumor is seen, usually on the bladder floor, either between or just above the ureteral orifices. The tumor has a cystic surface, bleeds easily, and is surrounded by a bullous edema. If doubt exists, a biopsy taken through the cystoscope will establish the diagnosis in the majority of cases. An endo-

metrial cyst of the left kidney in a 40 year old patient was reported by Marshall.[48] This patient had complained of swelling and pain in the left flank for 16 months. No relation between the menstrual cycle and the severity of the symptoms was established in the history. No evidence of pelvic disease was present, and there was no involvement of the peritoneum, Gerota's fascia, or renal capsule.

Treatment. No rule of thumb exists for the treatment of endometriosis. Each case must be individualized, and, perhaps, in this disease as in no other, the judgment of the physician plays a very important role. Many factors enter the picture, and influence the choice of method to be employed; the age of the patient, the extent of the lesions, the involvement of important structures and the ease of mobilization at operation, the desire of the patient for children, and the severity of the symptoms.

It is now well established that endometriosis is under the direct control of the hormonal cycle governing the menstrual cycle, and that the elimination of the ovarian hormones will cause a regression and atrophy of the endometriomas almost anywhere that they exist. It is a form of treatment that is almost always effective, but it is attended by the accompanying disadvantageous symptoms of the artificial menopause in younger women, and the cessation of the reproductive function in patients who might want to bear children. Castration, whether surgical or radiological, is a radical procedure to perform on younger patients afflicted with this disease. It is a procedure which can always be done in the event that there is progression of the disease or continuation of severe symptoms following more conservative attempts at arrest of the disease.

It is probable that many cases of endometriosis are never discovered. This indicates that many mild forms exist, and that in these no specific treatment is necessary. It is thought by many that incidental cases discovered at laparotomy should be treated. Doubtlessly, many early seedlings can be excised before fibrosis and scarring with deep invasion of adjacent organs have developed. Of course, no one can say that simple excision will prevent the development of other lesions, but this procedure is relatively simple with the abdomen already opened, and can be performed with little or no additional risk. Obvious chocolate cysts of the ovaries should be removed, but, with care, it is often possible to preserve normal portions of the ovaries. This is only of value if there exists no other evidence of endometriosis involving other structures, for as long as there remains any functioning ovarian tissue the lesions in the other organs may be activated. In this regard, it might be well to mention that hormonal therapy with any of the estrogens following castration for endometriosis is liable to be followed by reactivation of the disease. Counseller[69] has reported on the use of ovarian autografting for endometriosis, and claims good results in 4 of 5 cases in which the procedure was used. In his cases, however, all the diseased tissues were resected, and the grafts were used primarily to prevent or to control menopausal symptoms.

Endometriosis of the urinary tract frequently poses a difficult problem in treatment. It is generally conceded[25, 29,46,56] that transurethral fulguration has no place in the treatment of endometriosis of the urinary bladder. Of course, if the ureters are involved, the risk of excision is great. In all those cases in which a reasonable chance of resection of the endometrioma exists, whether by simple excision or by segmental resection of the bladder, the local procedure should be performed, especially if the patient has expressed

a desire for children. In those cases in which the hazards of resection tend to increase the operative mortality, a radical operation on the generative organs is the procedure of choice.

Jenkinson and Brown[39] have taken the stand of Cattell, whom they quote as having stated in 1937 that it was almost always necessary to remove both ovaries in a patient who presented deep lesions of the rectum and sigmoid. Mayo and Miller[49] and others[62,76] are also of this opinion. Some authors[80] believe that radiation castration is of value, but only if biopsy has confirmed the diagnosis. The treatment of intestinal obstruction caused by endometriosis is always surgical. A preoperative diagnosis will oftimes save the patient a resection of the bowel, and treatment will consist of bilateral oophorectomy and hysterectomy, with or without a temporary complementary colostomy if deemed necessary because of the degree of obstruction present. The therapy of ileal lesions will consist of internal decompression with the Miller-Abbott tube or similar device, restoration of fluid and electrolyte balance, followed by resection of the involved loop of ileum, and primary anastomosis. The performance of panhysterectomy and oophorectomy depends on the presence and degree of associated pelvic disease. If, however, the patient is desirous of a future pregnancy, and there is a reasonable chance thereof, and evidence exists indicative of fair ovarian function, a conservative operation on the ovaries might be performed, with resection of the involved bowel. McGuff, Dockerty, Waugh and Randall[51] claim that the prognosis of patients who have had obstruction of the bowel due to endometriosis is excellent. The chief factor in deciding whether to perform radical or conservative surgery on the ovaries is the desire for and possibility of future pregnancies. The possibilities for future successful pregnancies are not very good as a rule in the course of this disease. Low[46] was able to salvage only 9 children out of 249 cases, 90 of which were treated conservatively. Meigs[52,53] claims a pregnancy salvage rate of between 9 and 29%. Payne[64] salvaged pregnancy in 9% of his series; Lock and Myers[45] in 30%. The prognosis for increased fertility following therapeutic measures for endometriosis must certainly be guarded. Androgen therapy has been tried in the past several years with good success, especially when dealing with recurrences following the menopause or castration.[15,32] Miller[54] has used testosterone preoperatively to diminish the activity of the process so as to allow for radical surgery, and achieved excellent results without any masculinizing effects.

Summary. Endometriosis is a disease of women in the child-bearing age. It is of unknown etiology, although many theories have been advanced to explain its onset and pathogenesis. It is a disease very frequently associated with infertility and underdevelopment of the genital tract. Its manifestations are very protean, and it has been shown that almost every organ system of the abdomen may be the site of aberrant endometrium. Endometriomas have been found in the groin, and extremities, and may be experimentally transferred to the lungs, anterior chamber, and other organs of the body. The diagnosis is frequently easily made when a careful history reveals an acquired dysmenorrhea, pelvic pain, especially on jarring, and exacerbations at the time of the menses. Examination reveals characteristic shotty masses in the rectovaginal septum most easily palpated by rectum.

The treatment of this disease demands a high degree of judgment on the part of the surgeon. In single lesions involving only the serous coat of a given structure, it is frequently pos-

sible simply to resect the lesion. It is safer to err on the side of radicalism in treatment, however, than to attempt preservation of ovarian function when there is some involvement of both adnexae or when there is involvement of one adnexa and adjacent uterine wall. One exception to this, of course, is the case where the patient is very desirous of a future pregnancy. Conservative measures cannot be recommended for the relief of sterility, although they should be performed wherever possible in the hope that fertility might be restored. The reported salvage rate of subsequent pregnancies ranges from 9 to 30%. Patients on whom conservative measures are performed should be advised that future operative treatment might be necessary.

Endocrine therapy with the androgens has a very definite place in the treatment of this disease, but should be reserved for those cases which have recurrences of symptoms following castration, and in those few cases where a recurrence of symptoms develops after the menopause. Estrogens should not be used for control of menopausal symptoms for fear of stimulating any remaining lesions.[8,23,40]

The use of Roentgen-ray therapy in endometriosis has not been met with enthusiasm, for it is thought that a definite diagnosis must be made by biopsy before irradiation therapy is instituted.

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PEDIATRICS

UNDER THE CHARGE OF

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THE LIVER DISEASES OF INFANCY AND CHILDHOOD

A Brief Summary of Reports and Papers, 1934-1948

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VIRAL hepatitis, which became a major problem during World War II, is now being detected much more frequently in civilian populations over the world. The thought is growing that many patients with obscure liver disorders, infants and children as well as adults, have been ill with unrecognized viral hepatitis. With this concept in mind, and in order to clarify the types of liver disease which are actually encountered in the pediatric age period, a survey has been made of the papers on liver disease in infancy and childhood reported as such in the medical literature of the past 15 years.

Since in most cases the pathogenic agent is not known, the descriptions and classifications in the reports have been based almost solely on morphologic grounds. Apparently similar lesions have often been described under different names by different authors. Due to the difficulties involved in interpreting conditions of obscure origin, particularly when studied by others, little attempt is made in this review to alter the diagnoses as originally made by the reporting authors.

Tumors. *Cysts.* Solitary cysts of the liver have proved clinically important only when large enough to mechanically produce disturbing symptoms or to be physically detectable. White,[72] in 1936, described a huge cyst, apparently of bile duct origin, in a 4 month old male infant. In his discussion, White mentioned that less than 6 such nonparasitic cysts have been reported in the first decade of life. The majority of cysts are congenital in origin, and are classified as follows: (1) dermoids, (2) cysts lined with ciliated epithelium from primitive foregut, (3) lymphatic cysts, (4) bile duct cysts, (5) cysts of blood-vessel and endothelial origin. Atakam[5] described a congenital hepatic cyst in a 9 year old girl which was diagnosed as an ovarian cystoma and was surgically removed. Montgomery[46] described several clinically recognized cysts which he thought were probably of biliary origin. He stated that 25 out of 108 cases reported to date were in children under 13 years of age.

In this connection, mention should be made of congenital polycystic disease of the liver. In this disease, multiple cysts are scattered through the liver and usually through other organs as well.[4,67] The pancreas, kidneys,

spleen, ovary and lungs may also be affected. A discussion of the condition is given by Waterson and Morgan.[68] Ewing[19] states that the association of polycystic disease of the liver and kidneys may be found at autopsy in congenitally malformed infants, especially females.

Adenoma. Wilens[73] described a benign solitary hepatic adenoma in an 8 month old white male infant. Rupture of a dilated overlying vein necessitated surgery. At operation, the tumor was inoperable.

Cavernous Hemangioma (Hemangio-Endothelioma). These vascular tumors produce progressive abdominal swelling due to an enlarging liver. Gastrointestinal symptoms and anemia are frequent, whereas jaundice and ascites are infrequent.[39] One case report describes a 3 day old newborn infant who died of rupture of a cavernous liver hemangioma following difficult labor.[37]

Neuroblastoma. Two cases of hepatic neuroblastoma have been reported, the patients being infants.[23,56] In both, the histologic pattern was that of "sympathoma". A fibroblastoma of the liver has been described by Zuckerman.[80]

Primary Carcinoma. The usual presenting syndrome in the many reports is that of a progressive enlargement of the liver, either symmetrical or asymmetrical. Steiner[62] reviewed 105 reported cases in 1938, and felt that 75 presented enough positive evidence to justify the diagnosis. To these he added 2 personally observed cases: one, a 4 month old girl, the other, a 16 month old boy. Of the 77 patients, 41, or slightly more than half, were under 2 years of age at the onset. There were 51 boys and 24 girls, with the sex not recorded for 2 patients. Steiner thought that the frequent occurrence of the tumor at birth or in early infancy suggested that a congenital factor was important in its causation, at least in some cases. The symptoms were not characteristic, being dependent to a large extent upon the mechanical effects of the growth in the liver. Pain was a common symptom. There were frequent disturbances of nutrition, with anorexia, anemia, and loss of weight, although some children appeared well nourished. Jaundice and ascites occurred infrequently. The onset of symptoms was sometimes sudden, but more often insidious, with gradual slow enlargement of the abdomen. The average duration of life following the appearance of symptoms was 4 months. None of the patients survived. Steiner's classification of the cases according to the type of lesion is as follows:

Type of growth	Number of cases
Hepatoma	
Primary carcinoma (liver cell)	30
Adenocarcinoma (liver cell)	15
Carcinoma hepatocellulare solidum	2
Medullary carcinoma	5
	52
Cholangioma	
Primary carcinoma	3
Unclassified	
Primary carcinoma	22

Metastasis outside the liver occurred in 27.2% of the patients. Extension was sometimes into the portal and hepatic veins, and sometimes into the inferior vena cava. Metastasis to the lymph nodes occurred in 9 patients, to the lungs in 16, and to the pleura, pericardium, spleen and pancreas in 1 each. The tumor may spread within the liver by direct invasion of the capillaries, and at autopsy may be found widely disseminated.

Teratoma. Two instances of malignant hepatomas having teratoid features were reported.[50,70b] Sarcomatous, osteoid and cavernous areas were noted in these tumors. One patient with multiple tumors of the *hamartoma type* was also reported.[60]

Trauma and Rupture. In the newborn period, rupture of the liver is usually

ascribed to trauma, although infarction and hypoprothrombinemia have been deemed contributory factors in at least 1 case. Henderson's[30] review describes 47 cases of hepatic hemorrhage encountered in 1,312 postmortem examinations of stillborn and newborn infants, and summarizes the general manifestations of the lesion. The surface of the liver adjacent to the anterior abdominal wall was the site of the hemorrhage in most of the children. The incidence was higher in large infants and in prematures. Obstetrical abnormalities or difficult deliveries were concomitants in the majority of cases.

The sudden appearance of anemia in the first few days of life should make one consider rupture of a subcapsular hematoma.[35] The diagnosis of intraperitoneal hemorrhage can often be confirmed by paracentesis.

Extravasations beneath the capsule of the liver are fairly common in the newborn period. Most of the hemorrhages probably resorb without being clinically recognized. Only when the hematoma ruptures into the abdominal cavity are symptoms produced. Most cases are recognized after the development of this complication, or as incidental findings at autopsy or operation.

Subcapsular hemorrhage with rupture occurs also in older children, usually secondary to trauma, although a tumor or infarct may be the predisposing cause.[6,12] Bluish bronzing of the skin about the umbilicus may direct attention to the presence of blood within the peritoneal cavity.[6]

Abscess. *Bacterial.* Pyogenic abscesses of the liver have been reported by a number of authors. They may be secondary to umbilical infection of the newborn[40] or to an appendiceal abscess.[74] Those associated with septicemia are often multiple. Slesinger and Antiles[61] give an etiologic classification of pyogenic abscesses, derived from Kutsumai,[40] as follows:

Dysentery	43	Tuberculosis	11
Trauma	19	Umbilical infections	7
Mesenteric infections	17	Typhoid fever	6
Intestinal parasites	17	Influenza	2
Appendicitis	16	Unclassified	7

In this connection, mention may be made of Brim's[9] findings of postmortem liver cultures on 100 stillborn and dead newborn infants. *E. coli* was isolated from the liver in 3 and an anerobic streptococcus, a species of genus Bacteroides, and a gamma streptococcus in each of 3 others.

Amebic. Amebic abscesses, though rare, can occur in childhood.[64,65] The clinical manifestations differ little from those seen in adults, and the response to surgical drainage and anti-amebic medications is good.

Others. Liver abscesses due to ascaris lumbricoides,[59] echinococcus,[20] and trichomonas hominis[51] have been reported, as have multiple tuberculomata,[70c] and gummas and cirrhotic lesions in congenital syphilis.[41] Several instances of obscure granulomas in the liver have also been recorded.[14,26]

Infiltrations. *Xanthomatoses.* The liver, with its large number of reticuloendothelial cells, exhibits prominent infiltrations in the xanthomatoses. Several articles have stressed the liver infiltration. Weidman and Stokes[71] described a 4 year old white girl with extensive xanthoma tuberosum due to infectious cirrhosis. Wood[76] reported an unusual instance of primary liver carcinoma in an 8 month old white girl who, at autopsy, had lesions suggestive of Nieman-Pick's disease. The association of these 2 diseases was attributed to coincidence. Herbert's[32] patient was a 7 year old white girl with arrested growth, enlarged liver and spleen, renal disease with albuminuria and hypertension, and enormous increases in plasma phospholipids and cholesterol. She had repeated attacks of jaundice dating to 2 weeks of age, when a severe

umbilical hemorrhage had occurred.

Intracellular Liver Storage Diseases. Glycogen storage disease is the most commonly reported congenital disorder in which the liver cells seem unable to metabolize properly or utilize intermediary metabolic substances, which then accumulate within the cells. Good reviews of glycogen storage disease can be found in the papers by van Creveld,[66] Mason and Andersen,[44] Bridge and Holt,[8] and Manter and Bowman.[43] The variety of clinical and pathological observations has led Mason and Andersen, and also van Creveld, to suspect that the cases probably represent a group of different though related diseases rather than a single entity. Mason and Andersen, after a critical review of 68 cases, have proposed the following classification (condensed slightly from their paper):

Cases in which the main deposit of glycogen was in the liver (glycogen storage disease of the liver).

1. Primary defect probably a complete or a partial inability of the liver to transform glycogen into dextrose and possibly dextrose into glycogen (von Gierke's disease; 34 cases).

A. Rise in blood sugar after the administration of epinephrine less than 10 mg. per 100 cc. (15 cases).

B. Rise in blood sugar after epinephrine between 10 and 40 mg. per 100 cc. (11 cases).

C. No blood sugar curves after epinephrine reported but postmortem observations showed that the liver failed to break down its glycogen (2 cases).

D. No blood sugar curves after epinephrine and no postmortem enzyme studies reported but postmortem examination revealed a gross excess of glycogen in the liver and the kidney (6 cases).

2. Chronic galactosuria with hepatomegaly, with the liver apparently unable to metabolize galactose normally.

3. Fructosuria, with the liver apparently unable to form glycogen from levulose but usually without hepatomegaly.

4. Abnormal regulation of insulin in the body, with glycogen deposited in the liver.

A. Hyperinsulinism resulting from tumor of the islands of Langerhans with large amounts of dextrose given.

B. Diabetes mellitus with large amounts of insulin and dextrose given.

5. Unclassifiable in the preceding groups, sometimes because of inadequate data.

The characteristics common to most, if not all, cases of glycogen storage disease seem to be: (1) marked hepatomegaly, (2) fasting hypoglycemia with resulting ketosis, (3) little or no rise in blood sugar level following an injection of epinephrine, (4) high glycogen content in the liver, and (5) abnormal stability of liver glycogen after death. Secondary effects of impaired glycogenolysis are: (1) hypoglycemia which may induce ketosis, cerebral symptoms and possibly impair resistance to infections, (2) excessive conversion of carbohydrate to fat, which sometimes leads to obesity, and (3) negative nitrogen balance resulting from increased formation of sugar from protein and leading to impaired growth. Other evidences of liver disturbance include a defect in prothrombin formation, disturbance in methylation and, in infancy at least, lipemia. That the disorder may be familial is indicated by the report of Abramson and Kurtz[1] describing 4 fatal cases among siblings of one family.

Debré and associates[13] have emphasized that some children have chronic fatty enlargement of the liver in association with both disturbances of carbohydrate metabolism and hyperlipemia, and Kramer, Grayzel and Solomon[38] and others have described similar cases. These children may exhibit all the phenomena of glycogen storage disease along with the associated fat disturbance. Chemical examination of their livers reveals an unusually high fat content. Some have had a high glycogen content in addition, whereas others have had no such increase. Xanthomatous lesions may be present in the skin and elsewhere. A critical analysis

of the reported cases has been made by van Creveld.[66]

Hepatomegaly of Unknown Etiology. There are many reports in the literature of hepatomegaly of obscure origin occurring in children. McFarlane and Branday[49] describe 18 instances of painless abdominal enlargement due to an enlarged liver with ascites, seen in colored children in Jamaica. This is a chronic illness appearing in the age group 1 to 10 years, with intermittent fever, anorexia, jaundice and vomiting. Nutritional deficiency appears to be a contributing factor. Sometimes the spleen is enlarged as well, leading to a disturbance resembling Banti's syndrome. Several authors believe the pancreas may be responsible in some way for the hepatic enlargement.

Inflammation and necrosis due to poisoning. The liver is one of the chief detoxifying organs in the body. Most textbooks of pathology and pediatrics give an exhaustive list of diverse toxins which are known to cause liver inflammation or necrosis, perhaps followed by cirrhosis. Anesthetics, synthetic drugs, toxins of the infectious diseases, and naturally occurring poisons of plant and animal origin have all been implicated or at least suspected of being responsible for liver damage in some patients.

The identity of the noxious agent in any individual patient may not be clearly known, so that occurrence of some poisoning is often made solely on inferential grounds. In these circumstances it is always difficult to rule out viral hepatitis. Newborns as well as older infants and children may be affected.[42] Menten and Andersch[45] have reported 38 instances of liver disease among 299 necropsies of children who had been receiving sulfonamide therapy. Three had toxic necrosis, 9 had toxic central necrosis, and 26 had serous hepatitis and beginning toxic central necrosis. There was no correlation between the amounts of sulfonamide received and the liver lesions, and the relationship to the sulfonamides was not clear.

Henderson[31] has described various liver lesions in infants with erythroblastosis fetalis of severe degree. The incidence of cirrhosis of the liver was greater with the increasing length of survival of the affected children.

A number of cases have been reported of liver cirrhosis or necrosis among children due to alcohol,[54] bismuth,[75] mushroom poisoning,[24] copper,[21] and sulpharsphenamine.[17] Price[58] has suggested that barbiturates given to parturient women during labor may exert some toxic influence on the fetal liver.

Cirrhosis. Harrell and McBryde[28] classified the etiologic factors of cirrhosis of the liver in humans as follows:

Intoxication of cells by: Metals; organic compounds.
Obstruction to bile by: Congenital defects; tumors, stones.
Obstruction to blood by: Cardiac failure; venous thrombosis.
Infection: Of blood stream, of biliary tract; through effects of toxins.
Parasitism of: Blood; intestinal tract.
Diet and metabolic disturbance by: Alcohol; diabetes, hyperthyroidism.
Combinations of: Intoxication and infection; obstruction and infection.
Unknown causes.

Their report described 20 children with cirrhosis seen at the Duke Hospital, of whom 13 came to autopsy. Their conclusion was that the pathologic picture of cirrhosis in childhood resembled that seen in adult life, but classification is more difficult and often impossible. They suggest that the etiologic factors are often multiple.

Biliary Cirrhosis. An orthodox discussion of biliary cirrhosis in childhood is given in the paper by Evans[18] who divided this disturbance into 4 subgroups, as follows: (1) Congenital biliary cirrhosis with or without obliteration of ducts; (2) Infantile biliary

cirrhosis of Indian nurslings; (3) Acquired obstructive biliary cirrhosis—common duct obstruction; (4) Acquired non-obstructive biliary cirrhosis (Hanot's type). Most authors who have described individual cases of biliary cirrhosis, however, report them as such without subclassification. Biliary cirrhosis secondary to congenital aplasia of the extrahepatic bile duct system is much more common than the limited number of reports would indicate.

The diagnostic problems associated with the recognition of congenital defects of the biliary tract have been emphasized by Woolley,[77] who points out that there are no absolute methods for diagnosing these anomalies pre-operatively. Surgical exploration may reveal atresia of part or all of the extrahepatic ductal system, but biopsy specimens are needed for careful study of the liver architecture itself. Woolley comments that of a dozen infants in whom obliteration of extra-hepatic bile passages was strongly suspected, the diagnosis was confirmed at operation in only 3 instances. "The clinical laboratory . . . does not possess a critical test in this condition". The experience of the Reviewers corroborates that of Woolley.

Familial Cirrhosis. Cirrhosis of the liver occasionally develops in 2 or more children of the same family.[79] The liver lesions are variously described as hepatomegaly or hepatosplenomegaly, cirrhosis, portal cirrhosis, hepatic sclerosis and so forth. The condition may resemble Banti's disease.[48]

Atrophic cirrhosis. Dunsky[16] described a congenital biliary form of cirrhosis in a 2 month old white infant and stated that in infancy the biliary variety is more common than the portal variety. He cites several references to illustrate the frequent association of kidney lesions with this form of cirrhosis, and ascribes the kidney damage to injury from the unusual quantity of exogenous or endogenous toxins being excreted by it which the damaged liver had not been able to previously neutralize or detoxify. Braid and Ebbs,[7] Webster[70a] and Drummond and Watkins[15] have suggested that Rh incompatibility and lesions resulting therefrom may be responsible for the cirrhosis in some families.

Infantile Cirrhosis in India. Cirrhosis and other liver diseases are unusually common in India, and an abundant literature on the subject is accumulating.[11] Prabhu[57] summarizes the findings in 100 cases. The disturbance seems to be more common among Hindus. Its familial incidence is 20 to 30%. It is seen in the wealthy and middle class as well as among the poor. Children aged 1 to 2 years seem the most often affected. There is no sex predilection. Many writers believe that the diet is responsible but no convincing data are available on this point. Prabhu postulates an underlying familial or congenital defect. Infection may be important in the pathogenesis.

The liver disease as seen in India has an insidious onset with progressive liver enlargement, digestive symptoms, and mild hypochromic anemia. The course lasts 1 to 2 years and is usually fatal, but children who survive beyond 2 years often recover. Apparently the prognosis depends upon the extent of destruction of the liver substance during the early acute stages.

Other Cirrhotic Disturbances. There are reports suggesting that cirrhosis may be associated with disturbances in calcium and phosphorus metabolism, or with resistance to vitamin D.[22] Gillman and Gillman[25] have described liver damage in infantile pellagra. The liver is often sclerotic in erythroblastic (Mediterranean) anemia.

Amberg[2] divides juvenile cirrhosis into 2 forms. One is a biliary type, which is most common in children between 6 months and 2 years of age.

This is said to last 1 month to 1 year, and carries a high mortality rate. The majority of children under 1 year with cirrhosis have this variety, according to Amberg. In later years, the portal type of cirrhosis predominates. Infantile portal cirrhosis has a progressive course, and few cases have survived more than 5 years, according to this author. Ninety per cent of the children with portal cirrhosis have splenomegaly.

In reviewing the cases reported in the past 15 years, one finds that many authors simply describe cirrhosis of the liver in childhood without attempting an anatomic or etiologic classification. Many of the papers were written before the importance of viral hepatitis was appreciated, and most of the reports do not mention any possible relationship between hepatitis and cirrhosis.

Acute Yellow Atrophy. A number of reports of this syndrome have been recorded. The affected children have been of all ages, and the clinical course has usually been abrupt and fatal. Reports of acute yellow atrophy in children occurring in the course of small epidemics of catarrhal or infectious jaundice are of special interest.[33,78] Acute yellow atrophy is clearly not a disease entity, but a fatal syndrome which may complicate any type of severe liver damage.

Viral Hepatitis. Both infectious (epidemic) hepatitis and (homologous) serum hepatitis have received an abundance of attention in the past few years. Exhaustive review articles have been prepared by Neefe, Gellis, and Stokes,[52] Stokes,[63] and Havens.[29] Webb and Wolfe *et al.*[69] reported an increased incidence of infectious and homologous serum hepatitis in children during 1944, 1945, and 1946, and stated that non-icteric patients are more frequent than icteric ones. Apley and Wallis[3] concluded from their experience in England that serum hepatitis is rare in infancy. Parsons[55] reported an example of familial hepatitis in which 4 died of hepatic failure in the second decade of life, 2 are living with hepatic enlargement, 2 are alive and well, and 1 died probably of another cause. The early clinical picture of these cases was highly compatible with infectious hepatitis. Autopsy on 2 of those who died revealed peri-lobular and multi-lobular cirrhosis with areas of cellular regeneration. Dunsky,[16] Moon,[47] and others have described instances of familial cirrhosis among siblings, which may well represent sequellae to infectious hepatitis.

Whole blood, plasma, and blood products have been responsible for transmitting serum hepatitis in children as well as in adults.[10,36] However, no instance of serum hepatitis has been attributed to the administration of gamma globulin. On the other hand, fraction I (the anti-hemophilic fraction) of plasma, prepared according to the method of Cohn and co-workers, has been very recently shown to be capable of carrying the virus of homologous serum hepatitis.[63a]

Neefe and Stokes[53] reported an epidemic of infectious hepatitis which occurred at a summer camp in Pennsylvania. The epidemic was characterized by an unusually high attack rate. From the total camp group of 573, of whom about two-thirds were campers between 3 and 17 years of age, 44% developed hepatitis with jaundice, and an additional 17% had hepatitis without overt jaundice. The clinical picture of hepatitis in these children did not differ from that seen in adults. Epidemiologic observations and transmission experiments provided evidence that the agent responsible for this epidemic was waterborne, and was being excreted in the feces of persons with the disease.

Horstmann, Havens, and Deutsch[34] reported 2 institutional outbreaks of

infectious hepatitis involving children. One institution had 53 cases of hepatitis with jaundice and 56 cases of questionable hepatitis without jaundice. In the 2nd institution, 65% of 68 patients having hepatitis with jaundice were children under 16 years. The distinguishing features of infectious hepatitis as seen in these children were its mildness and short duration. None had a severe illness with prolonged jaundice or protracted convalescence. It would appear, however, that in childhood the clinical pictures of both infectious and homologous serum hepatitis are not greatly different from what is seen among adults, and the disease may vary in severity from subclinical disturbances at one extreme to rapidly fatal liver atrophy at the other.[27]

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As originally submitted this list contained 251 references; the authors kindly consented to reduce it to its present size in order to conserve valuable space.—Editor.

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The Oxidation of Ferrocytochrome-C by Peroxidase and Peroxides. BRITTON CHANCE,* Ph.D. (Johnson Research Foundation, Univ. of Penna.).

WHEREAS cytochrome oxidase has generally been recognized as the only physiological oxidant of ferrocytochrome-c, this paper shows that peroxidases from plants and from milk, in addition to the cytochrome-c peroxidase found in yeast by Altschul, Abrams, and Hogness,[1] can perform this oxidation in the presence of hydrogen peroxide or alkyl hydrogen peroxides.

Contrary to the negative results of Altschul, Abrams, and Hogness,[1] horse radish peroxidase†[1a] is an active catalyist for the oxidation of ferrocytochrome-c by hydrogen peroxide. In fact, at ferrocytochrome-c concentrations of about 1 x 10^{-6} M, this oxidation proceeds as rapidly as would the oxidation of the same concentration of pyrogallol which is usually used to measure peroxidase activity. A similar catalysis is observed when lactoperoxidase†[1a] is used.

The kinetics of the oxidation of ferrocytochrome-c have been recorded by a sensitive spectrophotometric technique[3] and are found to be unusual; the speed of the reaction is not proportional to the concentration of ferrocytochrome-c; the reaction velocity does not decrease rapidly until the concentration of ferrocytochrome-c has fallen to a rather low value. This is interpreted to mean that the rate of breakdown of a complex of peroxidase-peroxide and ferrocytochrome-c may be a limiting step in the catalysis. For this reason, the turnover number in this reaction is limited to about one mole of ferrocytochrome-c per mole of peroxidase per second at 25° C. and pH = 7.0. The corresponding figure for lactoperoxidase is 0.6. The corresponding figure for cytochrome-c peroxidase prepared from yeast was not given by Altschul, *et al*,[1] but appears to be considerably greater.

Some calculations have been made which show that the turnover number for the oxidation of ferrocytochrome-c by horse-radish peroxidase is compatible with the observed Qo_2 of slices of horse-radish root. The values of 40-100μ L/G(wet)/hour for horse-radish root[5] would correspond to a turnover of cytochrome-c of 0.5 to 1.25μM/sec. The peroxidase concentration is 50-175 P.E. per 200 g[2] and corresponds to 2.3 to 7.8μM. The required turnover number for peroxidase is about 0.1 times per second since one peroxidase-peroxide complex oxidizes two ferrocytochrome-c molecules. This value is well within the *in vitro* value above. The concentration of cytochrome-c in horse-radish root has not yet been measured, but based on Goddard's data[4] for wheat germ, a value on the order of 10^{-7} M may be expected. This is sufficient for peroxidase action.

The source of peroxide for such an oxidation is not known at present; however, several oxidase systems are recognized to reduce oxygen to hydrogen peroxide, xanthine oxidase, diamino oxidase, glucose oxidase,[6] and peroxidase itself in the presence of dihydroxymaleic acid and oxygen.[7]

Although no proof is offered that this mechanism of ferrocytochrome-c

* John Simon Guggenheim Memorial Fellow.

† Many thanks are due to Prof. H. Theorell and Dr. K. G. Paul for the loan of pure preparations.

actually occurs under physiological conditions, it is clear that cytochrome oxidase need be no longer taken to be the only catalyst in milk, plants, and yeast which can cause the oxidation of ferrocytochrome-c.

Physiology of the Breathing Impairment in Anthracosilicosis. HURLEY L. MOTLEY, Ph.D., M.D., and LEONARD P. LANG, M.D. (Dept. of Medicine Jefferson Medical College and Cardio-Respiratory Laboratory, Barton Memorial Division, Jefferson Hospital).

PHYSIOLOGICAL studies were made on more than 100 anthracite coal miners with respiratory complaints after prolonged exposure to dust. The breathing impairment may be classified in 4 main divisions: (1) decreased ventilation (maximal breathing capacity and vital capacity), (2) increased residual air (degree of emphysema expressed quantitatively as residual air percent of total lung volume), (3) disproportion between alveolar perfusion and ventilation (inadequate alveolar blood flow and reduced oxygen removal from inspired air), and (4) impaired distribution (unequal alveolar aeration) with mean pO_2 gradient between alveoli and arterial blood increased. Multiple involvement may occur contributing to the arterial blood changes (low pO_2, high pCO_2, and decreased oxygen saturation) and magnitude of hyperventilation. Except for poor distribution, the main compensatory mechanism is hyperventilation, which is adequate in the early stages and until loss of elasticity of lungs and chest wall structures restricts ventilation to the dyspnea level. The amount of hyperventilation without dyspnea varies widely. Fibrosis in some subjects, without a significant degree of emphysema and reduction in ventilation, results in unequal alveolar aeration and an increased percentage of poorly ventilated alveoli, producing an increased mean pO_2 gradient from alveoli to arterial blood and decreased arterial O_2 saturation. Studies with high and low levels of oxygenation indicate that the increased pO_2 gradient is primarily one of distribution and not a diffusion difficulty through the pulmonary membrane. Approximately two thirds of the patients had a significant degree of emphysema (residual air 35 to 65% of total lung volume). Vital capacity and maximal breathing capacity were of limited value in appraising the breathing impairment of patients with little or no emphysema but marked distribution impairment. The Roentgen-ray stage of silicosis was poorly correlated with functional change. No single test was satisfactory for correctly evaluating the breathing impairment in the group.

The Effects of Change of Position Upon the Cerebral Circulation of Man.* H. A. SHENKIN, M.D., W. G. SCHEUERMAN, M.D., E. B. SPITZ, M.D., and R. A. GROFF, M.D. (Harrison Dept. of Surgical Research, School of Medicine, and Graduate Hospital Univ. of Penna.).

THE cerebral blood flow and other cerebral functions were determined by the nitrous oxide method of Kety and Schmidt. A group of 5 normal persons were tilted head up 20 degrees from the horizontal and no change was noted in the cerebral blood flow. The mean carotid pressure dropped from an average of 88 to 73 mm. Hg. in this maneuver, and the cerebrovascular resistance decreased from 1.7 units to 1.4. A group of 6 patients with brain tumor were also tilted head up 20 degrees and here the cerebral blood flow diminished on the average from 51 to 36 cc./100g./min. The mean carotid pressure fell also in this latter group (from 92 to 86 mm. Hg.) but the cerebrovascular resistance increased by 25%.

* Aided by a grant from the U. S. Public Health Service.

A group of 4 normal patients were tilted head down 20 degrees from the horizontal. In this group the cerebral blood flow actually diminished by 14% although the mean carotid pressure increased 10%. The diminution of cerebral blood flow appeared to be occasioned by a 24% increase in cerebrovascular resistance. Four patients with brain tumor were tilted head down. No significant change in carotid arterial pressure, cerebral blood flow or cerebrovascular resistance were noted. A consistent decrease of cerebral oxygen consumption averaging 17% did occur.

The most plausible explanation for the alterations of cerebrovascular resistance in the normal state and the resultant maintenance of cerebral blood flow at normal levels is the assumption of a nervous control of the cerebral circulation. With this hypothesis the changes of pressure in the carotid vessels could serve as stimuli for reflexes that alter cerebrovascular resistance. In the brain tumor patients such reflexes are depressed and consequently the head up position causes a decrease in cerebral blood flow, and the head down position causes a far less marked reaction in the cerebrovascular resistance than is noted in the normal series.

In the treatment of brain tumor patients, it appears that the head up position is deleterious, insofar as it distinctly reduces the cerebral blood flow. The results of this investigation do not offer any objection to the head down position in the treatment of such patients, if it is desired to aid in the drainage of the upper respiratory tract or prevent aspiration of gastric contents.

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BOOK REVIEWS AND NOTICES

EVERYDAY MIRACLE. By GUSTAV ECKSTEIN. Pp. 235. New York: Harper & Brothers, 1948. Price, $2.75.

THESE essays, conclusive by faint implication only, are in the tradition of M. Henri Fabre. Observation is warmed by the observer's affection for the observed, and the reader shares in the writer's appreciation of individual canaries, chimpanzees, mice, cockroaches and macaws, trusting the accuracy of his briefly focused spotlight. Unlike M. Fabre, Dr. Eckstein has a literary sense of drama, which the great Frenchman escaped. E. T.

MEDICAL CLINICS OF NORTH AMERICA. Nationwide Number. Pp. 253; 33 ills. Phila.: W. B. Saunders, March, 1948. Price, $16.00 a year.

THIS volume is a symposium on diseases of the digestive system and covers in a concise practical manner most of the morbid states encountered by a gastroenterologist in this country. Bacterial and parasitic diseases are not included, except for amebic hepatitis and an article dealing with the possible relationship of amebiasis to indeterminate ulcerative colitis.

Emphasis is given to the controversial subject of vagotomy by including a clinical conference on this procedure.

The approach to all subjects is from the clinician's point of view with a minimum of discussion of theoretical aspects and of experimental data. This leads to easy reading and also makes this volume a valuable reference when one desires a quick clinical review of a subject. W. S.

THE THEOMATIC APPERCEPTION TEST. By SILVAN S. TOMKINS, Ph.D., Research Associate, College Entrance Examination Board. With the collaboration of ELIZABETH J. TOMKINS, B.A. Pp. 297. New York: Grune & Stratton, 1947. Price, $5.00.

THE author presents a careful, systematic approach to analysis of projective material obtained by use of the TAT. He stresses ideational content to the exclusion of formal or structural elements which Rappaport and others have found useful; but offers a more detailed method of study of such content than either Rappaport or Murray. The approach is eclectic. Most clinicians should find the method of TAT analysis found here quite useful.

The author begins with an all-too-brief history of the development of the test, mentioning only vaguely its relation to other projective techniques and to the concept of mental testing in general. He then proceeds with a discussion of reliability and validity, largely in terms of statistical coefficients, derivation of which is left entirely to the reader's imagination or to his enterprise in looking up the references given. In a short chapter on administration, general instructions are given.

The scoring system suggested by Tomkins is admittedly cumbersome and time-consuming and will probably prove more useful as an instrument for research than as a practical clinical tool. The elements included in the system, however, undoubtedly constitute a helpful guide and should be very useful if kept in mind while working with the test, even though most clinicians will find it inexpedient to use the system formally. Among the concepts employed in the scoring system are: (1) ten vectors; (2) seventeen levels or planes of psychological function; (3) twelve conditions or states imposed on the subject; (4) qualifiers—more specific aspects of either vectors, levels or conditions, e.g., temporal characteristics, contingency, intensity, causality, et cetera. There is a distinct gap in the relationship between the scoring system and the interpretation, which seems not to depend to any great extent on quantitative findings.

The bulk of the book is devoted to the problem of interpretation and includes many helpful sample stories. The material is considered in relation to: (1) family and home relationships; (2) love, sex, and marital relationships; (3) social relationships; (4) work and vocational setting. One of the most valuable chapters is that devoted to "Level Analysis" in which the relation between the story and the story-teller is probed. E. B.

HODGKIN'S DISEASE AND ALLIED DISORDERS. By HENRY JACKSON, JR., A.B., M.D., Asst. Prof. of Medicine, Harvard Medical School; and FREDERIC PARKER, JR., A.B., M.D., Assoc. Prof. of Pathology, Harvard Medical School. Pp. 177; 14 plates. New York: Oxford University Press, 1947. Price, $6.50.

THIS important and interesting monograph is based upon a combined clinical and pathological study made by the authors over many years. Much of the material brought together in this volume has appeared from time to time in several medical journals, but it has now been correlated and condensed and some new observations have been added.

The major portion of this treatise is devoted to a discussion of Hodgkin's disease, followed by shorter chapters on related conditions. Each chapter assumes the character of a brief original communication. Abbreviated case histories are used to illustrate the course of the disease, and excellent photographs represent adequately the pathological lesions.

The authors conclude, from their study of 259 cases of Hodgkin's disease, that the condition appears in 3 distinct forms or stages. These can be distinguished both clinically and pathologically. The first, termed by them Paragranuloma, is comparatively benign and is often localized for long periods to regional lymph nodes; the second, termed Granuloma, the common type, is much more serious for it is generalized and frequently involves the internal organs, being prone to affect the lungs, bones, spleen and intestinal tract, though it does not invade the nervous system; the third, termed Hodgkin's Sarcoma, is highly malignant and may invade any organ in the body including the nervous system. "Transitional forms of these three types of Hodgkin's disease occur, but it is essential for the understanding of the clinical features to recognize the existence of each." It has long been known that Hodgkin's disease may acquire the properties of an invasive tumor, but the conception set forth by the authors is in general novel.

They reiterate the statement that the presence of the Reed-Sternberg giant cells is always essential for the pathological diagnosis of Hodgkin's disease. They hold the belief, not generally current, that Hodgkin's disease arises in a single focus, usually but not always located in lymph nodes, whence it spreads or metastasises to distant organs. This view is important in relation to therapy for it offers the possibility of complete cure in an occasional case, particularly of the paragranulomatous type.

Of the related conditions next considered, reticulum cell sarcoma is regarded as a distinct entity, different from Hodgkin's disease sarcoma and lymphosarcoma. It may occur as a primary tumor of bone, of which they have observed 25 cases. Early amputation of the extremity, followed by radiotherapy, may be followed by recovery; this occurred in 6 of 11 of their patients. The view is expressed that lymphocytoma and lymphoblastoma arise exclusively in lymph nodes and usually acquire their serious nature only when leukemia or lymphosarcoma develops. Lymphosarcoma, of which they encountered 67 cases with 12 autopsies, is regarded as one of the rarest forms of "lymphoma"; for they restrict the term to those cases which present a single invasive and destructive tumor. Giant-Follicle Lymphoma tends frequently to undergo transformation into Hodgkin's sarcoma, lymphosarcoma or reticulum cell sarcoma. Of the authors' cases 36% developed lymphosarcoma. Plasmocytoma is considered particularly from the point of view of the extra osseous growths. The authors record 5 such cases in some of which intraosseous growths never appeared. Endothelioma receives little more than mention, since the authors have never encountered a case.

The monograph contains a wealth of valuable information based upon personal experience, and obtained from a wide knowledge of the literature. No effort has been made, however, to incorporate a comprehensive bibliography. References are given at the end of each section or chapter to those articles and treatises that have the most significant bearing on the subject under discussion. The book will become an essential text for all physicians and students interested in this field.

W. L.

DR. KIRKBRIDE AND HIS MENTAL HOSPITAL. By EARL D. BOND, M.D., Director of Research, Institute of the Pennsylvania Hospital. Pp. 163; 7 ills. Phila.: J. B. Lippincott, 1947. Price, $3.50.

THE life of Thomas Kirkbride, first Superintendent of the Pennsylvania Hospital for Nervous and Mental Diseases, is here presented in the light of his own times. The son of a rigid, parsimonious Quaker farmer, he became a doctor with the choice of specializing in surgery or psychiatry. His reasons for selecting psychiatry boiled down to settling his parents' peace of mind and knowing that his wife approved any plan of medical practice that would keep him close by. Out of such small beginnings Doctor Kirkbride headed a mental hospital that became an inspiration to countless numbers and started the Pennsylvania Hospital on its road to leadership in the management and housing of mental patients and in the organization of psychiatry. Doctor Kirkbride was one of the thirteen founders of the American Psychiatric

Association, later became president of the organization, and, as succinct evidence of his early inspirational example, he was followed in that same post of president by five other Pennsylvania Hospital psychiatrists.

The author, who is unusually qualified to record the life and times of Doctor Kirkbride, writes this biography as though he wished to present Kirkbride's personality in its living, throbbing environment; his descriptions of Philadelphia and Philadelphia medicine in Kirkbride's time are delightful. This historical and sociological presentation offers the reader true understanding and insight into the developing personality. Throughout, Doctor Bond compares Doctor Kirkbride's psychiatric ideals in the housing and care of the mentally ill with our so-called modern advances. The reader is bound to conclude that there is a long road ahead.

Anyone interested in psychiatry, Philadelphia medicine, or just Philadelphia, will find this book colorful and significant. M. P.

DERMATOLOGY IN GENERAL PRACTICE. By SIGMUND S. GREENBAUM, B.S., M.D., F.A.C.P., Prof. of Clinical Dermatology and Syphilology, Univ. of Pennsylvania Grad. School of Medicine, etc., etc., etc. In collaboration with: LESTER W. BURKET, M.D., D.D.S.; S. GORDON CASTIGLIANO, B.S., M.D., F.A.C.S; WILLIAM T. JOHNSON, M.D.; SAMUEL and HERBERT W. WADE, M.D. Pp. 891; 846 ills., 20 in color. Phila.: F. A. Davis, 1947. Price, $12.00.

THIS volume is "designed for the busy practitioner, the undergraduate, and for all those who from time to time may require information on the major clinical, diagnostic, and therapeutic facts about a particular dermatosis". It presents a large mass of material on dermatology which one might encounter in general practice; but it is doubtful if it is so presented that the information would be readily accessible to the general practitioner. This is due largely to the arrangement of the topic in alphabetic order which presumes that the practitioner is fully able to diagnose a given dermatosis, since the only way he can read up on the case would be if he knew under what diagnosis he might classify his patient's eruption. Granting this premise, he may still have trouble as some discases (e. g., lupus erythematosus) are discussed out of alphabetic order under their probable etiology (e.g., tuberculosis). A more useful arrangement for ready reference would be to place all the illustrations first and refer to the alphabetized text later. In this way, one might leaf through the pictures, find a probable diagnosis, and limit the search for appropriate material on a case to a few pages.

Aside from this major defect, there is much to recommend in this volume. It is well illustrated, up to date, and for the most part written in clear, concise language, with surprisingly few typographical errors. The sections on cancer, leprosy and oral diseases are exceptionally well done by able contributors. The presentation of pruritus is a valuable guide to the physician who is puzzled about what to do next for a patient with itching. Particular mention should be made of the data on eczema; vitamins; antihistamine substances; the treatment of acne vulgaris; the sulfonamides; the diagnosis of ringworm; the status of penicillin in dermatology and the relationship of peripheral vascular disease in dermatology. An example of the up-to-date material is the use of streptomycin in granuloma inguinale.

Other specific suggestions are: to add differential tables, e.g., on pigmentation; on the acute exanthemata, etc. The illustrations in the text, and if the present arrangement is maintained, should lie as near their text descriptives as possible. Furthermore, closer editing would prevent duplication of illustrations (figures 384 and 381 are identical, except for color). H. B.

THE PRACTICE OF GROUP THERAPY. Edited by S. R. SLAVSON, Director of Group Therapy, Jewish Board of Guardians, New York. Pp. 271. New York: Internat. Univ. Press, 1948. Price, $5.00.

THIS book will be of interest to those physicians who are looking for a way to relieve the emotional stresses of their patients. Group therapy requires an experienced leader. In groups of 7 to 20, patients are encouraged to free discussion of those feelings which usually they keep bottled up. Instead of the fixed pattern of family and society and condemnation for deviation, a therapy group is flexible and makes no demands.

There are 4 chapters on children, 4 on neuroses and behavior disorders, 1 each on psychoses, allergies and speech disorders.

The allergy group was made up of 10 allergic men and women and 10 other patients and met informally in a private home. Stenographic records were made from which excerpts are given. In free discussion, without advice, it became apparent that (some) patients used allergy to gain sympathy or to express hostility. The individuals improved in symptoms, in personal adjustments and in self-confidence. E. B.

AMERICAN MEDICAL RESEARCH PAST AND PRESENT. By RICHARD H. SHRYOCK, Ph.D., Prof. of History and Lecturer in Medical History, Univ. of Pennsylvania. Preface by JOHN F. FULTON, M.D. Pp. 350. New York: Commonwealth Fund, 1947. Price, $2.50.

ONE of a series of monographs published at the request of the Committee on Medicine and the Changing Order of the New York Academy of Medicine. The material is presented under the following headings: Formative Influences, Early Support of Research, 1860-1895, The Changing Economic and Social Background, The Era of Private Support, 1895-1940, Research Trends, Research Fields, Public Relations, Public Support, The Future.

The history of medical research in America, from its feeble beginnings in the middle of the 18th century to its present position of leadership, is traced in a most readable style. The book affords stimulating entertainment from start to finish and furnishes an excellent background for an unprejudiced appraisal of the present status of medical research in America.

This book should be read by everyone engaged in medical research in this country, if only to facilitate the visualization of his own field of endeavor in proper perspective. To all who are interested in the medical, social and economic development of America, the Reviewer heartily recommends this little volume.

D. C.

BENJAMIN SILLIMAN (1779-1864) PATHFINDER IN AMERICAN SCIENCE. By JOHN F. FULTON and ELIZABETH H. THOMSON. Pp. 294. New York: Henry Schuman, 1947. Price, $4.00.

BENJAMIN SILLIMAN occupies an unusual place in the history of American science. Although his original contributions were of a minor character, he probably accomplished more than did any other person in disseminating scientific knowledge and enthusiasms on both the popular and professional levels. A graduate of Yale College, Silliman was appointed to the first professorship of chemistry there in 1801 while still quite innocent of scientific training. He proved to be just the man for the post, not only because of intellectual ability but also because his personal tact, integrity, and enthusiastic industry were just the qualities needed for establishing science in an educational world still dominated by the classical tradition. In this respect, he was also aided by an honest but tolerant piety, which served to overcome the fears which science would otherwise have aroused at so orthodox a center as New Haven.

So equipped, Silliman prepared for his career by securing training in chemistry and medicine at the University of Pennsylvania, and by spending a stimulating year in Europe. Returning to Yale in 1806, he served there for half a century, guiding two generations of able students and founding scientific institutions which were of national as well as local importance. He was not only the first professor of chemistry at Yale, but the first to teach geology in the United States (1806). In 1810 he led in the founding of the Yale Medical School. Displaying a genius for organization and for raising what were then substantial funds, he secured for Yale collections in geology and in the fine arts. In 1818 he established the *American Journal of Science* ("Silliman's Journal"), which became a clearing house for the scientific interests of the nation. In 1846 he persuaded the College to set up the first courses in science independent of the Arts College, an arrangement which led later to the beginnings of the Sheffield Scientific School and to a Graduate School which gave the first American Ph.D. (1863).

While engaged in all these activities, Silliman also found time to serve as a consulting mining engineer and as a very successful popular lecturer. Although there was already a tendency to separate pure and applied science, and to isolate basic science from the public, Silliman was opposed to this by both temperament and conviction. Not a technical specialist, he valued science primarily as a means for economic progress and for popular enlightenment. In this respect, he may be viewed as one who preserved the scientific outlook of the preceding century while at the same time he did so much for the institutions of the future.

Dr. Fulton and Miss Thomson have based this biography on a thorough use of the great mass of Silliman papers, as well as on materials found in other collections. Their treatment is a sympathetic one, tempered by objectivity. The result is a most happy combination of careful scholarship and human interest, calculated to widen the horizon of any reader concerned with the development of the sciences in this country.

R. S.

ORAL VACCINES AND IMMUNIZATION BY OTHER UNUSUAL ROUTES. By DAVID THOMPSON, O.B.E., M.B., Ch.B., D.P.H., Director of the Pickett-Thomson Research Laboratory, ROBERT THOMPSON, M.B., Ch.B., Patho-

logist, St. Paul's Hospital, London, and JAMES TODD MORRISON, M.D., D.P.H. Pp. 329. Balt.: Williams & Wilkins, 1948. Price, $11.00.

THIS book brings together in 1 volume the results of many researches on oral vaccines and attempts at immunization by other nonparenteral routes. The summaries of over 1000 research papers are given in chronological order, but at the end of most chapters the authors have attempted to sum up the evidence and to give just and unbiased conclusions. Part I contains general information on oral immunization. Part II gives data on the oral method of immunization against numerous infectious diseases; pollinoses, and poison ivy dermatitis; the use of staphylococcal, streptococcal, gonococcal, *B. coli* and *B. pyocyaneus* oral vaccines; the use of oral vaccines in certain animal diseases; and passive oral immunization with placental extracts and seroplasma. Part III is limited to the oral prophylaxis with toxins and toxin-antitoxin mixtures, and Part IV lists attempts at immunization by other unusual routes. All the references to the literature are listed alphabetically in the back of the book. There are also author and subject indices. Those interested in the subject of immunization will find this a useful volume. H. M.

INTRODUCTION TO THE HISTORY OF SCIENCE. Vol. III (in 2 parts). *Science and Learning in the 14th Century.* By GEORGE SARTON, Associate in the History of Science, Carnegie Institution of Washington. Pp. 2154. Balt.: Williams & Wilkins, 1947, 1948. Price, $20.00.

THIS really colossal undertaking has already resulted in 3 large books—Vol. 1 (839 pp. covering the period from Homer to Omar Khayyam) appearing in 1927; and Vol. 2 (1251 pp. covering the 12th and 13th centuries) appearing in 1931 in two books but with continuous pagination and a single index. Now after 17 years, the 14th century is covered by Vol. 3, divided in the same way as Vol. 2. Thus one scholar, working for some 36 years, has brought to fruition his vast and unique plan of bringing into one work the scientific and cultural record of the civilization of the world up to the time of the Renaissance. Truly a Gargantuan "Introduction"!

The author's original purpose, "to explain the development of science across the ages and around the earth," is pursued in these two books on the lines laid down in the earlier two volumes. As this plan is complicated, he facilitates their use by explaining their construction. Each deals with one half of the 14th century and the two are symmetrical; that is, each has 14 chapters, the first of which is a synthesis of the other 13. These 13, each of which has the same title as its vis à vis in the other book, are on such topics as Philosophical and Cultural Background, Medicine (these 2 being the largest), Education, Chemistry, and so on. They are packed with countless factual items, impossible for extended consecutive reading, nor are they intended for such. The first chapter of each part, on the other hand, each consisting of more than 300 pages and subdivided into the same sections as are the subsequent 13 chapters, amalgamates into a scholarly readable story the knowledge of the period in each field of endeavor. These 2 survey chapters are obviously the author's favorite part of the work, to which the rest play subordinate if necessary supporting roles. From these and from his Introductory Chapter, readers will learn much about the intellectual activities of the 14th century and the unifying bonds between different countries, a special emphasis being given to the contributions of Eastern thought.

The General Index requires 373 large double columned pages, and even so is followed by shorter indices in Greek, Chinese and Japanese characters. In true Sartonian manner, the General Index is described as not only "relatively complete" for Vol. 3, but also "a very rudimentary repetition" of the indexes of the first two volumes. As has been noted elsewhere, the extensive index and bibliographical notes make the work of very considerable use as a dictionary and a bibliography of the period, but these are by-products and should not detract from its greater role as "an integration of the intellectual doings" of the scholars and scientists of the 14th century.

Even to erudite scholars, and with due allowance for assistance received, the author's encyclopedic knowledge must seem prodigious. One wonders who could write an adequate critical review of these volumes except Dr. Sarton himself. Let us hope with him that, even if he has now concluded the undertaking 5 centuries short of his original goal, he may be found to have pointed the way for others to carry on the task. E. K.

PATHOLOGY OF TUMOURS. By R. A. WILLIS, D. Sc., M.D., F.R.C.P., Prof. of Human and Comparative Pathology, Royal College of Surgeons, London. Pp. 1050; 500 ills. St. Louis: C. V. Mosby, 1948. Price, $20.00. PROFESSOR Willis' previous book, "The

Spread of Tumors in the Human Body" is rightly regarded as one of the significant contributions to the literature on oncology. The present larger and more comprehensive work deals with all aspects of neoplasia and neoplastic diseases, and is, as the author states, the outcome of his special interests in tumors during 20 years as a hospital pathologist.

The book is addressed primarily to pathologists, research workers and senior students, but Professor Willis expresses the hope that "clinicians also may find it useful and even elementary students may find it intelligible." This hope is amply justified. The book gives not only a well balanced and readable account of present day knowledge, but also constitutes an invaluable record of the authors' own observations and conclusions. Many brief reports of personally studied cases are introduced as examples; on controversial matters, while indicating that they are controversial, Professor Willis has plainly stated his own present opinion; the figures, of which there are 500, are all from material which he has studied personally.

The first part of the work (about 200 pages) deals with general aspects of tumors, such as definition, classification and nomenclature, the proper meaning of "innocence and malignancy," the experimental production, statistical study, mode of origin, structure and growth, spread, and modern hypotheses as to the nature of tumors. The author's conviction that much has yet to be learned from the comparative pathology of tumors is reflected not only by a separate chapter on tumors in animals, but by sections in the chapters which are devoted to tumors in the different organs. Part I ends with a recapitulation of the subjects discussed and the conclusions reached.

Part II of the work is concerned with what is sometimes referred to as special oncology: a systematic consideration, first of the epithelial tumors, malignant or benign (somewhat over 400 pages); then of the mesenchymal tumors, including those arising from lymphoid and other haemopoietic tissues (approximately 150 pages); the tumors of neural tissues (approximately 100 pages), and finally sundry special classes of tumors such as melanomas, embryonic tumors of viscera, teratomas and chorioepitheliomas (approximately 100 pages). The reference lists are carefully chosen; as the author says, he has preferred to base his discussion on what he has read himself; many of the references are annotated, as "a valuable review of the physical and chemical properties of tumor cells, including a discussion of their invasiveness." The text is well printed; the index is good. The book is warmly recommended. The pathologist will find in it much of interest, for it expresses clearly and frankly the opinion of a distinguished fellow pathologist; the student of medicine will find it a good guide to a difficult subject, and the clinician an excellent and readable work of reference. B. L.

HEART. By ALDO A. LUISADA, Instructor in Physiology and Pharmacology, Tufts College Medical School. Pp. 653; 352 ills. Balt.: Williams & Wilkins, 1948. Price, $10.00.

THE author stresses the physiologic basis for normal and abnormal functions of the heart and circulation. The characteristics of and reasons for symptoms and physical signs are well demonstrated by graphic methods. The separation of chapters on the basis of an anatomical rather than an etiologic classification is admirably suited for this purpose. The use of mechanical aids to diagnosis, especially phonocardiography, is extensively illustrated. Rare and unusual forms of heart disease are covered scantily or not at all. No attempt is made to discuss advanced electrocardiography. This book is recommended especially for its clear descriptions of normal and abnormal cardiovascular physiology and the use of technical aids in understanding these problems. C. K.

A HISTORY OF THE HEART AND THE CIRCULATION. By FREDRICK A. WILLIUS, M.D., M.S., Prof. of Medicine, Mayo Foundation, and THOMAS J. DRY, M.S., Assoc. Prof. of Medicine, Mayo Foundation. Pp. 456; illustrated. Phila.: W. B. Saunders, 1948. Price, $8.00.

THE numerous books on historical and cultural aspects of medicine that have appeared since the War give a good indication of the interest that the medically inclined public—at least in publishers' opinions—has in this field. Anthologies and systematic treatises, both general and in special fields, present ever increasing opportunity for contact with the concepts, achievements and personalities of our past.

The present volume, one of the best in a field in which it has several predecessors, offers its material in 3 main divisions. The first and longest part (268 pp.) presents the story in 8 chronological divisions that increase in length from the earliest, Antiquity (23 pp.) to the latest, the First Quarter of the Twentieth Century (45 pp.). The second section gives in more detail 20 arbitrarily selected "Special Biographies" (ranging from Hippocrates to Sir Thomas Lewis) of men who have already appeared in the earlier part.

The third section, "The Chronologic Presentation of Data According to Subject," presents 18 tabulated chronologies of such subjects as Aneurysm, The Pulse, the Anatomy, the Physiology, the Therapy of the Heart and Circulation, Milestones in Medical Education (not restricted to the special field of the heart) and so on. This unusual arrangement, in addition to requiring considerable repetition, produces many breaks in continuity. Osler, for instance, is given 2 pages in the general history, then 10 in the biographical section, with mention in several of the chronological lists. Resultant inconveniences are minimized, however, by good indices.

Among the many illustrations, there is a refreshingly high percentage, especially in recent times, of newcomers to historical texts. The welcome emphasis on the modern here and throughout the volume, not only results in an allocation of text space more proportional to the actual progress made but also provides all the more information that is not to be found in out of print histories. It is perhaps needless to add that the work is not a History in the professional historian's sense, and it is probably not meant to be, but it does appeal to the Reviewer as an adequate and entertaining account of the progress of one of the most important fields of human medicine.

E. K.

No Retreat From Reason and Other Essays. By Alfred E. Cohn. Pp. 279. New York: Harcourt Brace, 1948. Price, $3.50.

The author of this group of essays has been consistently a vigorous advocate of the intellectual attitude toward life. His faith is based upon the progressive use of intelligence to solve man's problems and to achieve happiness and the good life.

The essay which names the collection presents an optimistic appraisal of our opportunity in the confused and turbulent world we find about us. Its calm and reasoned approach is entirely wholesome. Several of the essays deal with the interaction of the method of science and the achievements of the arts. The analysis of this interaction has long been a favorite field of inquiry for the author and he has contributed significantly to it. Three essays are biographical appraisals of men of medicine; two of them men of recent years; the other, Harvey. A chapter entitled "On Retiring" is a delightfully humorous interlude, nevertheless permeated with thought-provoking philosophy.

J. A.

The Metabolic Brain Diseases and Their Treatment in Military and Civilian Practice. By G. Tayleur Stockings, M.B., Late Deputy Medical Superintendent, City Mental Hospital, Birmingham, England. Pp. 262; 3 ills. Balt.: Williams & Wilkins, 1947. Price, $4.50.

This book is a re-interpretation of the schizophrenic, delusional, and affective psychoses, using a new, simpler terminology and classification, which is based on the results of the latest research in neurophysiology and psychiatry, plus 5 years extensive experience with insulin and electroshock ("neurometabolic") therapy in treating mental casualties of World War II. The author presents a remarkably unified and cogent concept of the psychoses as diseases of brain metabolism (encephalopathies) affecting either one or both of the 2 fuels of the brain cells—oxygen and glucose. The largest portion of the book is then devoted to a very thorough discussion, using this concept, of these disorders, presented much in the same way that a textbook in internal medicine would describe pneumonia, giving etiology, diagnosis, course, prognosis, and therapy, with an explanation of how the therapy works. By thus tying mental symptoms to disorders of biochemistry and the physiology of the brain, he brings the pathophysiology of psychoses into line with such psychosomatic diseases as essential hypertension, and establishes their treatment as rational and not empirical.

This is an extraordinary and possibly revolutionary book, which may become a milestone in psychiatry. It deserves a wide audience.

J. S.

Medical Research In War. Report of the Medical Research Council for 1939-45. Pp. 455. London: His Majesty's Stationery Office, 1947. Price 7/6 net.

This report, covering the War Period is the first to be published by the Council in 8 years. So widespread are the ramifications of Council promoted activities that a fair picture emerges of British medical research in war time. The work was carried out in the National Institute for Medical Research or in the Council's 21 External Research Establishments or through grants to individuals, and Fellowships. It covered such broad fields as Wounds and War Injuries, War Diseases, Therapeutics (including penicillin), Nutrition in War Time, Personnel, Research, Health in Industry, Preventive Medicine, Laboratory and Clinical Studies in the various specialties, Cell Growth, Genetics, Radiant Energy.

The excellent record of this government created body since its incorporation in 1920, and of its predecessor The Medical Research

Committee, should be of special interest to the American medical profession in these days of coordinated research and increasing governmental participation. E. K.

EXPERIMENTAL AIR-BORNE INFECTION. By THEODOR ROSEBURY, with the co-authorship of the staff of the Laboratories of Camp Detrick, Md. Pp. 222; 40 figs. Balt.: Williams & Wilkins, 1947. Price, $4.00.

THIS first Microbiological Monograph of the Society of American Bacteriologists presents results of investigations of experimental air-borne disease released by the Biological Warfare Service. Between December 1943 and October 1945 Dr. Rosebury with 11 co-authors and 16 mentioned assistants conducted investigations on Air-Borne Infection at Camp Detrick, Maryland, forecast by his report printed a few months ago in the Journal of Immunology. Disease was induced in small animals inhaling droplet nuclei aerosols of *Brucella suis,* Psittacosis virus (Borg), Psittacosis virus (6BC), *Malleomyces pseudomallei, Malleomyces mallei,* Meningopneumonitis virus (Cal 10), and *Pasteurella tularensis;* the report does not indicate whether the list is complete but states, "work with infective agents was begun 21 March, 1945 and continued until shortly after the end of the war." These protocols occupy one-tenth of the volume.

The remaining nine-tenths of the book records the procurement of equipment and secret training for a study of experimental air-borne disease. The first part describes elaboration of apparatus for safe exposure of animals to aerosol suspensions of virulent organisms in droplet nuclei. The second describes certain selected atomizers for producing infective aerosol clouds. The third part discusses their modification of the Greenburg dust impinger for bacterial sampling. Since alteration of critical dimensions sacrifices impinging efficiency, the authors state "that the sampler operates as a bubbler rather than as an impinger in the strict sense"; bubblers are much less efficient collectors of droplet nuclei than impingers. Yet the violence of this type of impinger may, by destroying delicate organisms, as the authors suggest, perhaps account for the small lethal dosage (one-third) obtained by British investigators of Biological Warfare; quantitative precision is illusive.

Nevertheless the mortality patterns parallel previous results on air-borne influenza and streptococcal infection of mice in that geometrical increases in dosage tend to yield arithmetic increases in mortality, and the work provides valuable new evidence of the vulnerability of animals to inhaled droplet nuclei infection. W. W.

RHEUMATISM AND SOFT TISSUE INJURIES. By JAMES CYRIAX, M.D., B.Ch. (Cantab.), Physician-In-Charge, Physiotherapy Dept., St. Thomas's Hospital, London. Pp. 410; 107 ills. New York: P. B. Hoeber, 1947. Price, $9.50.

ACTUALLY a work on physical therapy, particularly on massage and manipulative techniques, this book gives an excellent description of the physical management of various muscle and joint conditions. "Treatment by movement has been substituted (for rest) for many traumatic and rheumatic lesions in the course of the present century. Movement may be applied in various ways . . . active and resisted exercise, forced movement, and deep massage."

The sections discussing muscular spasm and fibrotic nodules are well thought out. The plates and figures are well done and interesting, although in many cases the techniques illustrated are dubious in value or even dangerous—such as manipulation of the cervical spine for rheumatoid spondylitis.

Why treatment of conditions of the alimentary tract, of herpes zoster and of retraction of the nipple should be included in this work is something of a mystery. Many of the terms used are confusing and the conditions described are somewhat garbled, particularly the descriptions of functional conditions, such as "psychogenic spasms," "sciatic scoliosis," "capsulitis," etc. The book shows little organization from the standpoint of disease entities, but is loosely organized from the standpoint of parts involved and treatments for each area. The section on rheumatoid arthritis is rather confusing in its arrangement, and the symptomatology and diagnostic criteria are sketchy and incomplete.

It is felt that this book would be of limited value to a general practitioner or an internist, because of its sketchy method of describing the diseases of the joints and muscles, and because of the emphasis on manipulative techniques which should be carried out only by an expert in physical therapy, if at all. It can be taken, however, as a reference work for massage and manipulative techniques, and for diagnostic criteria for the more obscure soft tissue injuries. J. H.

SOURCE BOOK OF ORTHOPAEDICS. By EDGAR M. BICK, M.D., F.A.C.S., Orthopedic Surgeon, Mt. Sinai Hospital, New York. 2d ed. Pp. 540; 31 ills. Balt.: Williams & Wilkins, 1948. Price, $8.00.

DR. BICK after 10 years has brought out another edition of his Source Book which is an enlarged and much more valuable history of the development of Orthopaedic Surgery. This is a most interesting book, weaving the advances of the specialty around the personalities connected with the various affections of bones and joints, and integrating into it the more recent developments. This broad concept has been difficult to crystallize into book form, as the author frankly admits; but Dr. Bick is to be congratulated upon producing an interesting history of orthopedic surgery. His extensive bibliography attests to his wide reading and preparation in making this edition even more valuable than the first.

P. C.

MEDICOLEGAL PROBLEMS. Edited by SAMUEL A. LEVINSON, M.D., Ph.D., Univ. of Illinois College of Medicine, for the Committees of the Institute of Medicine and the Chicago Bar Association. Pp. 255; 6 ills. Phila.: J. B. Lippincott, 1948. Price, $5.00.

THE first aim of this book is to provide both medical and legal professions with an understanding of the viewpoints of the other, so that judicial review may be honest and fair. Secondly, it brings together both professions so that conditions requiring legislative action may be undertaken. And lastly, the legal liability of the physician in various situations is clarified.

The phases covered are: the medical witness and the Minnesota plan; artificial insemination; medicolegal pathology, sterility operations; trauma and tumors; scientific tests in evidence. Each problem is covered medically, legally, and the discussion following each presentation is included. The treatment of each phase is satisfactory and enlightening. It is of importance for the physician to realize the conservatism of the benh, and the difficulty (in some states) of establishing medical tests and facts as incontrovertible evidence.

G. R.

DISABILITY EVALUATION. By EARL D. MCBRIDE, B.S.M.D., F.A.C.S., Diplomate American Board Orthopedic Surgery. 4th ed. Pp. 667; 400 ills. Phila.: J. B. Lippincott, 1948. Price, $12.00.

THE fact that this is the 4th edition of this extensive work is its best commentary. There is no other book in English that covers the subject in such a complete and comprehensive way.

One could easily find fault with minor matters, such as the treatment of the hysterias, the neuroses and malingering, and object that from the psychoneurotic aspect of injuries the subject is treated from the standpoint of the employer.

The traumatic neurosis should be considered as a definite entity, as an actual clinical disease process, if one would be fair to the plaintiff. If this were done, it would add definitely to the value of the book. It is not fair to pick out such a highly technical and specialized subject as nervous diseases and psychiatry and more particularly the functional group when this needs a special volume for its interpretation. The author's composite schedule of approximate evaluations for partial permanent disability, which has been given a prominent position in the book, will prove of great value in compensation cases. The large number of line and photographic illustrations, all of them particularly well done, add tremendously to the book's value.

It should be in the hands of both doctors and lawyers interested in workmen's compensation and transportation damage suits. It will also be of value to the ordinary physician who is asked to testify in damage and compensation cases. It is a splendid book of reference.

D. McC.

PSYCHOBIOLOGY AND PSYCHIATRY. By WENDELL MUNCIE, M.D., Assoc. Prof. of Psychiatry, Johns Hopkins Univ. 2d ed. Pp. 620; 70 ills. St. Louis: C. V. Mosby, 1948. Price, $9.00.

THIS new edition of this valuable presentation of the teachings of Adolf Meyer, seen through the clinical experiences of Dr. Muncie, omits many of the blank spaces of the 1st edition but adds many new facts.

The 3 parts of the book consider the normal chiefly through personality studies of medical students, the abnormal with chapters on each mental disease or defect, and treatment in general and for particular abnormal reactions.

As Adolf Meyer's terms have not been adopted by others, they do not add much to the reader's comfort. But the basic concepts are so original, sweeping and dignified that they deserve a place in any psychiatrist's thinking. And their spirit is indicated in a quotation from William James, "Experience exceeds logic, overflows and surrounds it".

E. B.

NEW BOOKS

Advances in Biological and Medical Physics. Vol. I. Edited by JOHN H. LAWRENCE and J. G. HAMILTON, Univ. of California. Pp. 484. Illustrated. New York: Academic Press, 1948. Price, $8.60.

Cancer Manual. Standards for the Diagnosis and Treatment of Cancer. By the CANCER COMMITTEE of the Iowa State Medical Society. Pp. 160. Iowa City: Athens Press, 1948. Price, $1.00.

Hetero-specific Alteration Therapy. By S. NUKADA, M.D., Ph.D., and C. RYU, M.D., Nukada Institute and Sanatorium. Pp. 80; 5 ills. Tokyo, Japan: The Japan Medical Publications Co., 1948. No price given.

Diagnosis in Gynaecology. By JAMES V. RICCI, M.D., Clinical Prof. of Gynaecology and Obstetrics, New York Medical College. Pp. 259. Phila.: Blakiston, 1948. Price, $4.50.

Rural Health and Medical Care. By FREDERICK D. MOTT, M.D., and MILTON I. ROEMER, M.D., M.P.H. Pp. 608. New York: McGraw-Hill, 1948. Price, $6.50.

Vitamine und Vitamintherapie. Von DR. MED. EMIL ABERHALDEN, Univ. Zurich. Pp. 408; 42 ills. Bern, Switzerland: Hans Huber, 1948. Price, Fr. 28.

The Engaged Couple Has a Right to Know. By ABNER I. WEISMAN, M.D. Pp. 256. New York: Renbayle House, 1948. Price, $3.00.

Pharmacology and Therapeutics in Nursing. By MARION SYLVESTER DOOLEY, M.D., and JOSEPHINE RAPPAPORT, R.N., B.S. Pp. 444; 26 ills. New York: McGraw-Hill, 1948. Price, $3.75.

Corazon Pulmonar e Insufiencia Coronaria. Por el DR. JUAN GOVEA, de la Facultad de Medicina de Paris. Pp. 178; 70 ills. Havana, Cuba: M. V. Fresneda, 1948. No price given.

The Healthy Hunzas. By J. I. RODALE. Pp. 263; 16 ills. Emmaus, Pa.: Rodale Press, 1948. Price, $2.75.

The food and farming habits of a people dwelling on the northwestern border of India.

Treatment of Heart Disease. By WILLIAM A. BRAMS, M.S., M.D., Ph.D., Assoc. Prof. of Medicine, Northwestern Univ. Pp. 195; 11 ills. Phila.: W. B. Saunders, 1948. Price, $3.50.

Chemistry in Nursing. By RAYMOND E. NEAL, Assoc. Prof. of Chemistry, Simmons College. Pp. 564. New York: McGraw-Hill, 1948. Price, $4.00.

Advances in Protein Chemistry. Vol. IV. Edited by M. L. ANSON, Continental Foods, Inc., and JOHN T. EDSALL, Harvard Medical School. Pp. 575; 13 ills. New York: Academic Press, 1948. Price, $8.50.

An Introduction to the History of Dentistry. By BERNHARD WOLF WEINBERGER, D.D.S. In 2 vols. Pp. 514 and 408; 177 and 136 ills. St. Louis: C. V. Mosby, 1948. Price, $20.00.

NEW EDITIONS

Human Neuroanatomy. By OLIVER S. STRONG and ADOLPH ELWYN, College of Physicians and Surgeons, Columbia Univ. 2d ed. Pp. 442; 336 ills. Balt.: Williams & Wilkins, 1948. Price, $6.00.

WE welcome a new edition of Human Neuroanatomy, by Professors Strong and Elwyn, for it is one of the best and most ably written books in a large field on this subject. The first edition was developed from chapters on the nervous system which, for years, had been incorporated in Bailey's Histology. (It was reviewed in this Journal **206**, 809, 1943.) The 2d edition has been improved by addition of one new chapter and enlargement of another.

The new Chapter X, on Segmental and Peripheral Innervation, employs several new illustrations, principally from an excellent small clinical book by Haymaker and Woodhall. The expansion of Chapter XXI is notable. The account of the blood supply of the brain, especially the blood vessels of the basal ganglia and internal capsule, is splendid.

This book is for the advanced or more serious student of neurology. Some aspects of it are too heavy for the neophite. This is not an adverse criticism, but rather one of the inadequate time available for study of neuroanatomy in many medical schools. W. W.

HOSPITAL CARE OF NEUROSURGICAL PATIENTS. By WALLACE D. HAMBY, M.D., F.A.C.S., Prof. of Neurology and Neurologic Surgery, Univ. of Buffalo School of Medicine. Springfield, Ill.: Charles C Thomas, 1948. 2d ed. Pp. 156, 30 figs. Price, $3.00.

THIS is a very satisfactory little book. It reviews briefly and concisely, the major types of cases seen on a neurosurgical service. The preoperative care and the special tests to be employed in each group of cases are carefully outlined. The major postoperative complications together with the proper method of handling them are well described. The format and appearance of the book is pleasing. Residents, internes and nurses connected with a neurosurgical service can read this book with profit. F. G.

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